OBSERVATIONS ON THE PATHOLOGY OF RHEUMATIC DISEASES.

with particular reference to the value of biopsy in diagnosis and assessment of treatment.

A thesis, presented for the degree of Doctor of Philosophy by Bruce Cruickshank, M.B., Ch.B. (Edin., 1943).

PREFACE.

The research described in this thesis was carried out in order to assess the value of histological examination of certain tissues in the diagnosis of several rheumatic diseases and in assessing the results of treatment.

The " rheumatic diseases " include a variety of conditions which have in common pain in limbs, joints, or the connective tissues of the trunk, and the absence of bacterial infection of affected tissues. They may be classified as follows :-

a) Conditions in which arthritis is the predominant feature - rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and gout,

b) conditions in which arthritis is a prominent feature, but less significant than the presence of lesions in other tissues - rheumatic fever and systemic (disseminated) lupus erythematosus, and

c) conditions in which arthralgia or myalgia are prominent clinical features - poly-arteritis nodosa, dermatomyositis, scleroderma and fibrositis.

No observations on fibrositis have been made in the present study, in which the emphasis is largely on the changes found in rheumatoid arthritis. For the sake of brevity, the remaining diseases in the group are frequently referred to as " other rheumatic/

rheumatic diseases."

Much interest has been shown in the histopathology of the rheumatic diseases during the last decade. Diseases such as rheumatoid arthritis, which had previously been considered to be predominantly articular, have been shown to affect several other tissues. Thus, claims have been made that specific lesions occur in the joints, subcutaneous tissue (as nodules), muscles and nerves and that the histological examination of such tissues is of value in establishing the diagnosis. These claims have been disputed, so that the diagnostic value of histological examination is not clearly defined. The establishment of a Rheumatic Research Unit at the Northern General Hospital, Edinburgh, provided the opportunity of collecting some of these tissues, e.g. nodules and muscles, and the routine material passing through the Pathology Departments of the University and Royal Infirmary, Edinburgh, proved a ready source of synovial tissue and nerves. Lesions occurring in each of the tissues in rheumatic diseases have been compared with lesions occurring in that tissue in the absence of rheumatic disease. These comparisons indicated that a very few lesions, such as the tophi of gout, were diagnostic by themselves. None of the lesions found in the other diseases were specific, but when all the features of the cases were assessed, it was possible to reach a definite diagnosis in most of the cases studied.

While/

While the research was in progress, cortisone and ACTH were introduced into clinical medicine. The dramatic clinical response which these hormones produce in the rheumatic diseases raised the question whether the clinical improvement of the patient was accompanied by changes in the histopathology. It thus became important to assess whether examination of tissues before and after treatment with such hormones could give any indication about their affects. It was found that the naturally occurring lesions in most of the diseases and tissues studied were such as to make such serial examinations of very limited value.

Although intended to assess the value of examination of tissue obtained during life, much of the material studied was obtained at autopsy. It is felt justifiable to include such material since living patients are likely to be encountered, whose disease state corresponds exactly with that of these deceased patients. The inclusion of the autopsy cases resulted also in the study of another aspect of the pathology of one of the more important rheumatic diseases, namely, the cardiac lesions of rheumatoid arthritis. There is a discrepancy between the results of clinical and pathological studies of this subject and the conclusions drawn from several pathological investigations have varied. It was hoped, therefore, that a review of the changes in some 60 cases of the disease would help to elucidate their significance.

The/

The following publications contain material which appears in this thesis :-

1. The Histopathology of Diarthrodial Joints in Ankylosing Spondylitis - 1951, Ann. Rheum. Dis., 10, 393. The synovial lesions reported in this paper are described in Section I.
2. Focal lesions in Skeletal Muscles and Peripheral Nerves in Rheumatoid Arthritis and other Conditions - 1952, J. Path. Bact., 64, 21. This is a much shortened version of Sections III and IV combined.

Section II of the thesis is based on a paper read to the Heberden Society on December 7th 1951 and will be published in the July 1952 number of " The Annals of the Rheumatic Diseases." A shortened version of Section VI was read to the Edinburgh Pathological Club in May, 1951.

Acknowledgements.

The work reported in this thesis has been made possible by the tenure during the period of supervision (1949-50) of a Research Grant from the Nuffield Foundation, and the facilities made available in their respective Departments, by Professors A. Murray Drennan and L.S.P. Davidson, for all of which the writer is deeply indebted. Dr. J.J.R. Duthie, Senior Lecturer in Rheumatic Diseases, has made available all the facilities of his Research Unit at the Northern General Hospital and has also given much helpful advice and criticism. Similar/

Similar criticism and advice has been given on many occasions by Dr. R.F. Ogilvie, Professor A.C.P. Campbell and Dr. D.H. Collins. Grateful thanks are due to Sister N. Baillie and the Nursing Staff of the Rheumatic Research Unit for their help in the many minor surgical operations carried out. Physicians and surgeons of all units in the Royal Infirmary, Edinburgh Northern Group of Hospitals, Bangour Hospital, Bridge of Earn Hospital (Orthopaedic Unit) have given access to and permission to quote from their case notes. Thanks are due to their Secretaries and to the Records Officers of these hospitals for help in tracing such records. Many past and present members of the teaching staff of the Pathology Department have helped in collecting material. The technical work and photographs have been carried through by Mr. T.C. Dodds and his assistants to whom many thanks are due. Acknowledgement is due also to Professor G.H. Percival for allowing access to material in his Department, to Professor Sir James Learmonth and Mr. K. Paterson Brown for providing specimens of muscle, to Mr. D.L. Savill for many specimens from cases of ankylosing spondylitis, and to Professor S.L. Baker and Drs. H.J. Gibson, E.G.L. Bywaters, H.F. West, G.J. Hackett, J.P. Kulka and H.T.G. Strawbridge for various specimens of subcutaneous nodules.

CONTENTS.

Results/

SECTION I.

The Value of Histological Examination of Synovial Tissue in the Diagnosis of Rheumatic Diseases.

INTRODUCTION.

It is largely an open question whether the synovial tissue of joints, bursae and tendon sheaths shows changes which are specific to any of the rheumatic diseases. In some of the diseases, such as ankylosing spondylitis, systemic lupus erythematosus and polyarteritis nodosa, this is due to a lack of adequate studies of the histopathology, whereas in others such as rheumatoid arthritis different authorities disagree about the interpretation of the changes. Most workers agree that the appearances in osteoarthritis, gout and rheumatic fever are usually characteristic. The object of this section of the thesis is to record the findings in synovial tissue in the rheumatic diseases in comparison with those in non-rheumatic diseases, such as septic arthritis, non-specific tenosynovitis and traumatic lesions such as torn menisci. It will be shown that no specific lesions occur in rheumatic diseases, with the exception of those found as the result of urate deposits in gout.

The first detailed descriptions of the changes in/

in the synovial tissue of joints in rheumatoid arthritis were given by Nichols and Richardson (1909), who drew a clear distinction between the lesions in rheumatoid arthritis and those in osteoarthritis. These and other early papers (Strangeways, 1918 ; Fisher, 1924) did not attach any specificity to the features seen. However, Allison and Ghormley 1931(a)) laid great stress on the occurrence of lymphocytic foci in rheumatoid arthritis and regarded them as peculiar to that disease. Since then there has been much disagreement about the significance of the changes in rheumatoid arthritis, much of the argument being concerned with the interpretation of these foci. Key (1934) described lesions in traumatic synovitis which were basically the same as those in rheumatoid arthritis, and similar features had been noted previously by Wallace and Permar (1927). On the other hand, Ghormley and Deacon (1936) regarded the foci as a specific reaction to an abnormal, probably chemical stimulus.

During the next decade, most of those who studied synovial tissue regarded the foci as non-specific (Lawson , 1936 ; Inge, 1938 ; Jordan, 1938 ; Kling, 1938 ; Bennett, 1941), but Fisher (1937) stated that the changes in the later stages of rheumatoid arthritis were specific. Bennett examined material from 1,000 cases of joint disease and found foci in conditions other than rheumatoid arthritis. In a later paper (Bennett, 1943), the lesions/

lesions of rheumatoid arthritis were compared and the conclusion drawn that the usual appearances are sufficiently different to indicate that the two conditions were entities of different pathogenesis. Klinge (1932) has previously stated that the changes in these two diseases differed only in degree. Ghormley and Brav (1933) and Young and Macmahon (1935) noted that apart from tubercles, which are not always easy to find, the appearances in tuberculous synovitis are very similar to those of rheumatoid arthritis. Freund (1933) described changes in non-gummatous syphilis which are the same as those of rheumatoid arthritis. Weber (1944-5) mentioned the non-specificity of the lymphocytic foci, pointing out that the lesions illustrated by Allison and Ghormley were merely germinal lymphoid follicles.

More recently Rosenberg (1949) and Collins (1949 (a) & (b)) have stressed the diagnostic value of the appearances in rheumatoid arthritis. Collin's conclusions were based on the study of synovial tissue in 250 cases of joint disease. He regarded as diagnostic a combination of hyperplasia of the synovial tissue and villi, hyperplasia of the cells lining the surface, congestion, oedema and massive lymphocytic and plasma cell infiltration with large foci, provided the specific features of other diseases such as tuberculosis are absent. Bennett (1952) in discussing Collin's paper (1949, b) again expressed his opinion that the lesions of rheumatoid/

rheumatoid arthritis are not diagnostic and Gibson writing in the most recent textbook on rheumatic diseases (Fletcher, 1951) referred to the absence of diagnostic criteria for rheumatoid arthritis.

With regard to bursae in rheumatoid arthritis, Rosenberg (1949) described three types - small adventitious bursae over bony prominences, hygromatous bursae and bursae arising from the fusion of multiple subcutaneous nodules. Adventitious bursae have only an incidental association with the disease being lined with hyaline connective tissue. Hygromatous bursae (ganglia) show the same appearances as tendon sheaths. The only other reference to the lesions of bursae in rheumatic diseases which could be found was in Klinge's monograph (1933(a)) This author described a case of isolated olecranon bursitis in which the histological features were mainly non-specific granulation tissue. Because of the occurrence of "fibrinoid" necrosis in the wall, the lesions were regarded as rheumatic.

Clinical involvement of tendon sheaths occurs in approximately 40 per cent of cases of rheumatoid arthritis (Kellgren and Ball, 1950) and in most cases the lesions resembled closely those in the synovial tissue of joints (Bennett, 1943; Collins, 1949 (b); Kellgren and Ball). The conclusions of Bennett and of Collins about the specificity of tendon sheath lesions were the same as in the joints./

joints. Swift (quoted by Collins, 1936 and 1939) noted that changes similar to those seen in the tendon sheaths in rheumatoid arthritis occurred in isolated traumatic tenosynovitis in young persons. Much of the confusion regarding the pathology of tenosynovitis arises out of the assumption of Klinge (1932 and 1933) and other German writers (See Albertini, 1929) that cases of isolated tenosynovitis in which the histological pattern resembles that of rheumatoid arthritis are of rheumatic origin. It should be noted, however, that rheumatoid arthritis may commence as tenosynovitis (Baumgartner, 1946).

Certain syndromes which were previously regarded as separate entities are now accepted by most authorities merely as variants of rheumatoid arthritis. Thus the changes described in the synovial tissue in juvenile rheumatoid arthritis (" Still's Disease") were the same as those in the adult form of the disease (Klinge, 1933(b); Portis, 1938; Angevine, 1942; Langley, 1945; Prichard, 1947). Cases of rheumatoid arthritis with leukopenia and splenomegaly ("Felty's Syndrome") had joint lesions similar to those of typical rheumatoid arthritis (Bach and Savage, 1940; Talkov et alii, 1942; Hatch, 1945). The cases so far studied have been at a late stage and the synovial changes have been in keeping with this, i.e., mainly fibrosis. The joint lesions in cases of rheumatoid arthritis with psoriasis were the same to those of typical rheumatoid/

rheumatoid arthritis according to Nordin (1934) and Bauer et alii (1941). On the contrary, Hench (1948) believed that some of these cases differ from rheumatoid arthritis proper in showing polymorphs and haemorrhage in the synovial tissue. However, the presence of polymorphs in acute cases of typical rheumatoid arthritis is a recognised feature (Fisher, 1929) and old or recent haemorrhage is frequently seen in that condition. The lesions of synovial tissue in " Reiter's Disease " were believed by some writers to be distinguishable from those of rheumatoid arthritis (Bauer and Engleman, 1942; Hollander et alii, 1945) whereas Wepler (1942) and Hench (quoted by Hollander et alii, 1945) believed such differentiation to be impossible. The lesions described by Porter and Lonergan (1932) in intermittent hydrarthrosis were also very close to those of rheumatoid arthritis.

There are very few reports on the histology of synovial tissue in ankylosing spondylitis. Polley and Slocumb (1946) mentioned biopsies from the hip and shoulder, stating that the histological appearances were those of rheumatoid arthritis. Boland (1949) mentioned similar appearances in biopsies from three joints (site not stated). These findings together with the fact that peripheral joints in 8 - 18 per cent of cases show clinical features like those of rheumatoid arthritis (Dekkers, 1943; Boland and Present, 1945) is the basis for the current opinion that ankylosing spondylitis is merely/

merely a variant of rheumatoid arthritis (Dawson and Tyson, 1938; Goldberg, 1944; Collins, 1949 (c) ; Rosenberg, 1949).

The synovial lesions of pure osteoarthritis are generally regarded as invariable fibrosis, variable vascularity and minimal round cell infiltration (Nichols and Richardson, 1909 ; Sawyer and Ghormley, 1941; Bennett et alii, 1942). However, occasional mention has been made, of a more marked inflammatory picture with round cell foci (Parker et alii, 1934; Key, 1936; Kernwein and Lyon, 1942). Such changes are much more frequent and pronounced when the osteoarthritis is superimposed on a preceding inflammatory lesion (" mixed" arthritis) and Ghormley (1938) stated that local collections of round cells are never found in osteoarthritis except under these circumstances.

Although the specificity of the reaction to the urate deposits in gout has never been questioned, the occurrence of cases with clinical appearances similar to those of late rheumatoid arthritis has been known for very many years (Virchow, 1868; Litten, 1876; Moore, 1887). Pathological examination of such cases has shown fibrous ankylosis with urate deposits (Lang, 1937; Ludwig et alii, 1938; Kersley et alii, 1950) but changes in synovial tissue were not described. Collins (1938(a)) noted that the proliferative changes in synovial tissue in some cases of gout simulated those of rheumatoid arthritis. Sherman (1946) described/

described granulation tissue along with urate deposits in a case of seven months' duration.

Most writers on the pathology of synovial tissue in rheumatic fever stress the occurrence of focal lesions analogous to the Aschoff bodies of the heart (Coombs, 1911 ; Fahr, 1921(a); Swift, 1924; Klinge, 1932 and 1933(a)). Bennett (1943) examined joints from eleven cases but was unable to find focal lesions in any of them. Apart from the focal lesions, the changes described have been intense non-specific acute inflammation in the early stages (Collins, 1949 (d)) or congestion, oedema and mild lymphocytic infiltration. Involvement of tendon-sheaths was reported by Murphy, (1945) who described and illustrated marked proliferation of surface cells and round cell infiltration. The specificity of the changes in this disease would appear to depend on the presence of the focal lesions.

Only three brief references could be found to the pathology of synovial tissue in systemic lupus erythematosus. Tremaine (1934) examined the knee in one case, finding hypertrophy of villi and perivascular inflammatory cells throughout the sub-synovial tissue and capsule. Ginzler and Fox (1940) described slight hyperplasia of the cells lining the surface and a small piece of fibrin on the surface as the only abnormalities in the one knee which they examined. Lowman (1951 (a)) referred to round cell infiltration of venule walls and fibrosis of the synovial tissue in five cases. None of these writers/

writers published illustrations of the synovial lesions. Clinically, this condition resembles either early rheumatoid arthritis or rheumatic fever, but deformities of the type seen in late rheumatoid arthritis are rare (Slocumb, 1940 ; Bywaters, 1949; Lansbury, 1949). Fletcher (1951) observed that polyarthritis in this disease may precede involvement of other systems by years.

The only reference which could be found to the lesion of synovial tissue in polyarteritis nodosa is the abstract of a paper read to the American Rheumatism Association (Lowman, 1951 (b)). This author described the occurrence of lesions similar to those seen in other tissues in the disease.

MATERIAL AND METHOD.

A. Joints.

Synovial tissue from joints has been studied from 59 cases of rheumatoid arthritis, consisting of specimens from 84 joints. In 42 cases material was obtained from one joint only, in 11 cases from two joints, in 4 cases from three joints and in 2 cases from four joints. The anatomical distribution of the joint material is shown in Table I. Multiple blocks were available from 35 joints, comprising 28 knees, 3 shoulders, 3 elbows and 1 proximal interphalangeal joint. Whenever possible they were taken from the suprapatellar pouch, the medial or lateral compartment and the infrapatellar fat pad. An additional block was sometimes taken to include/

Table I.

Anatomical Distribution of Synovial Tissue from Joints in Rheumatic Diseases.

Diagnosis	Total Cases	Total Joints	Joints											
			Shoulder	Acromio-Clavicular	Elbow	Wrist	Metacarpo-phalangeal	Proximal inter-phalangeal	Distal inter-phalangeal	Hip	Knee	Ankle	Posterior intervertebral	Sterno-clavicular
Rheumatoid Arthritis	59	84	9	1	6	1	7	9	1	3	47			
Ankylosing Spondylitis	8	11								7	3			1
Osteoarthritis	27	31	1							16	7	1	5	1
Gout	2	5				1	1				1	1		1
Rheumatic Fever	11	14	1		1					1	11			
Systemic Lupus Erythematosus	4	8					1	1			6			
Polyarteritis Nodosa	3	5	1								4			
Total	114	158	12	1	7	2	9	10	1	27	79	2	5	3

include one or other meniscus and in nine cases two adjacent blocks were taken from one or other of the regions mentioned. Thirty one of the cases were examined post mortem and provided material from 54 joints : eighteen of the autopsies were carried out by the writer. In the remaining 35 cases, the tissue was obtained at one or more operations from 29 joints.

Synovial tissue obtained from 74 joints in 55 cases of other rheumatic diseases was also studied. This consisted of 11 joints from 8 cases of ankylosing spondylitis, 31 joints from 27 cases of uncomplicated osteoarthritis, 5 joints from 2 cases of gout, 14 joints from 11 cases of rheumatic fever, 8 joints from 4 cases of systemic lupus erythematosus and 5 joints from 3 cases of polyarteritis nodosa. The anatomical distribution of this material is shown in Table I. Blocks were taken as in rheumatoid arthritis. Practically all the material from ankylosing spondylitis and osteoarthritis was obtained at operation, whereas the other cases were all studied post mortem.

The above specimens were compared with tissue from a single joint in 146 cases of non-rheumatic disease, comprising 41 cases of non-specific synovitis, 7 of loose bodies in joints, 7 of septic arthritis, 4 of osteochondritis, 28 of torn menisci, 19 of cysts of menisci, 2 of haemophilia, 35 of tuberculous arthritis, 2 of syphilitic arthritis and 1 of amyloidosis of the knee. The anatomical distribution/

distribution of these cases is shown in Table II. Most of this material was obtained at operation and was filed in the collections of the Pathology Departments of the University and Royal Infirmary. In the majority of cases only one or perhaps two sections were available.

B. Bursae.

Tissue from bursae was studied from 7 cases of rheumatoid arthritis, 114 of non-specific bursitis and 6 of tuberculous bursitis.

C. Tendon Sheaths.

Tissue from tendon sheaths was studied from 4 cases of rheumatoid arthritis, 2 of systemic lupus erythematosis, 75 of non-specific (excluding stenosing) tenosynovitis and 27 of tuberculous tenosynovitis.

In all cases, the blocks were embedded in paraffin and sections were cut and stained with haematoxylin and eosin. For comparative purposes the occurrence of the features considered by Collins (1949 (b)) as diagnostic of rheumatoid arthritis was recorded. The presence or absence of necrosis and fibrosis was also noted. In rheumatoid arthritis, the total duration of the disease and the duration, clinical activity and stage (Steinbrocker et alii, 1949) in the joints studied was recorded.

RESULTS.

A. Joints.

Rheumatoid/

Table II.

Anatomical Distribution of Synovial Tissue from Joints in Non-rheumatic Diseases.

Diagnosis	Total Cases	Joints							
		Elbow	Metacarpo-phalangeal	Proximal inter-phalangeal	Hip	Knee	Ankle	Metatarso-phalangeal	Sterno-clavicular
Non-specific Synovitis	41		2	1	1	35			2
Loose Bodies in Joint	7					7			
Septic Arthritis	7			1		3	1	2	
Osteochondritis	4					4			
Tears of Menisci	28					28			
Cysts of Menisci	19					19			
Haemophilia	2					2			
Tuberculous Arthritis	35	3			3	29			
Syphilitic Arthritis	2					1			1
Amyloidosis	1					1			
Total	146	3	2	2	4	129	1	2	3

Rheumatoid Arthritis.

The combination of lesions regarded as diagnostic of rheumatoid arthritis by Collins (Figs. 1-6) was seen in 24 joints (Table III). In 13 of the joints necrosis was seen in addition to the other features (Figs. 7 & 8). Fibrosis, usually of fine degree was seen in seven of the joints (see later section). Atypical features which were present in addition to the "diagnostic " combination included abnormal numbers of polymorphs (Fig. 9) or plasma cells, the latter sometimes containing Russell bodies (Fig.10).

Thirty joints showed evidence of activity, but lacked one or more of the above criteria (Table IV). Thus in some joints, all the features were present except villous hyperplasia (Fig. 11) and in others the inflammatory infiltration was of moderate or slight degree. Necrosis was present in 10 of these joints. Fibrosis was seen in 17 joints and though sometimes fine, was usually more active and more extensive than in the previous group. One joint showed unusually cellular fibrosis with rather loose round cell infiltration (Fig. 12). Two joints in this group showed lesions resembling the subcutaneous nodule of rheumatoid arthritis rather than the usual lesions (Cases 20 and 33, Fig. 13).

In 24 joints the most prominent feature was old-standing fibrosis (Table V). This was accompanied in some cases by slight proliferation, in one by healed arteritis and in another by metaplasia/

Table III.

Synovial Tissue from Joints in Rheumatoid Arthritis showing " Diagnostic " Pathological Features.

Case No.	Joint	Total Duration	Affected Joint			Necrosis present as well as other features.
			Duration	Stage	Clinical Activity	
4	acromio-clavicular	10-12 yrs.	?	?	Active	-
	knee		?	II	Active	-
5	knee	20 yrs.	?	?	Inactive	-
6	knee	18 yrs.	? 1 yr.	III	Active	+
7	shoulder	2 yrs.	< 2 yrs	II	"	-
15	elbow	13 yrs.	< 13 yrs	III	"	+
17	elbow	32 yrs.	2 yrs.	II	"	-
18	knee	2½ yrs.	2 yrs.	II	Inactive	+
19	knee	10 yrs.	< 10 yrs	II	Active	+
23	L. knee	8 yrs.	< 1 yr.	II	"	-
29	hip	?	?	?	?	+
30	elbow	?	?	?	?	-
32	knee	?	?	?	?	+
34	shoulder	?	?	?	?	+
38	knee	3 yrs.	?	?	?	-
39	elbow	9 yrs.	3 yrs	?	Active	+
40	knee	?	?	?	Inactive	+
43	wrist	1 yr.	5 mths	I	Active	-
44	metacarpo-phalangeal	?	2 yrs.	II	"	+
	prox. inter phalangeal		2 yrs.	II	"	+
45	hip	17 mths	17 mths	?	"	+
49	knee	7 yrs.	2 yrs.	II	"	-
51	knee	10 yrs.	2½ yrs	II	"	+
54	knee	11 yrs	?	?	"	-

Synovial Tissue in Rheumatoid Arthritis.

Fig.1. Case 5. Knee (lateral compartment) x 35. Increase in number and size of villi which contain large capillaries and large foci of lymphocytes. The focus to right of centre has a germinal centre. Fibrosis is also seen. See also Figs. 2 and 4.

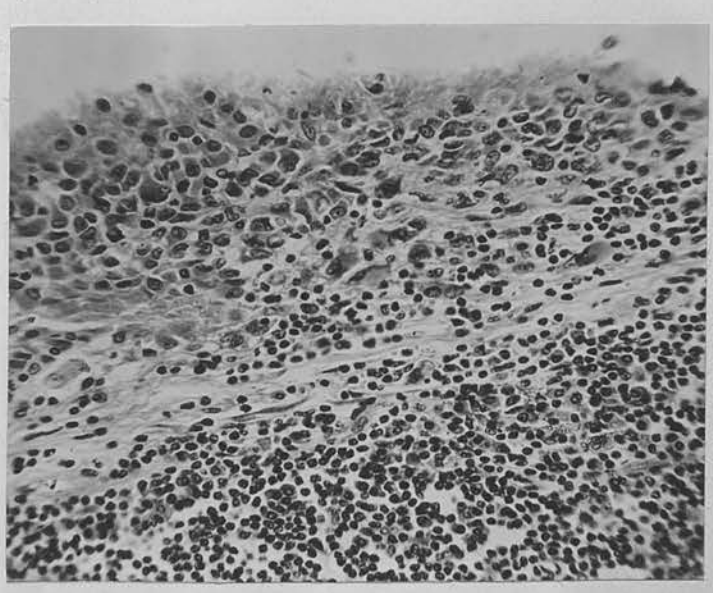

Fig.2. Case 5. Knee. x 250. Another field from same section as Fig.1, showing hyperplasia of lining cells some of which are multinucleate. Dense infiltration of underlying tissue with lymphocytes, plasma cells and histiocytes. These cells are present in smaller numbers among the synovial cells. See also Fig. 4.

Synovial Tissue in Rheumatoid Arthritis.

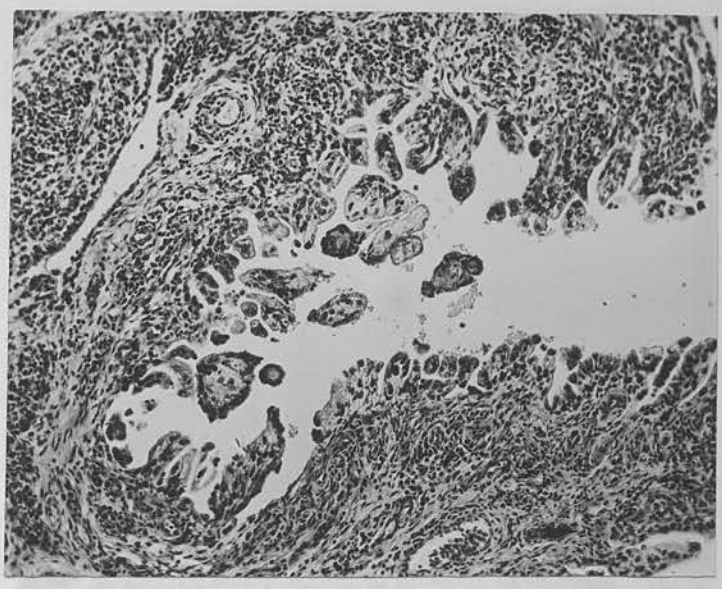

Fig.3. Case 39. Elbow. Hyperplasia and oedema of lining layer with many papillary processes. Massive infiltration of underlying tissue with lymphocytes and plasma cells. Many capillaries. See also Fig. 7. (x 100).

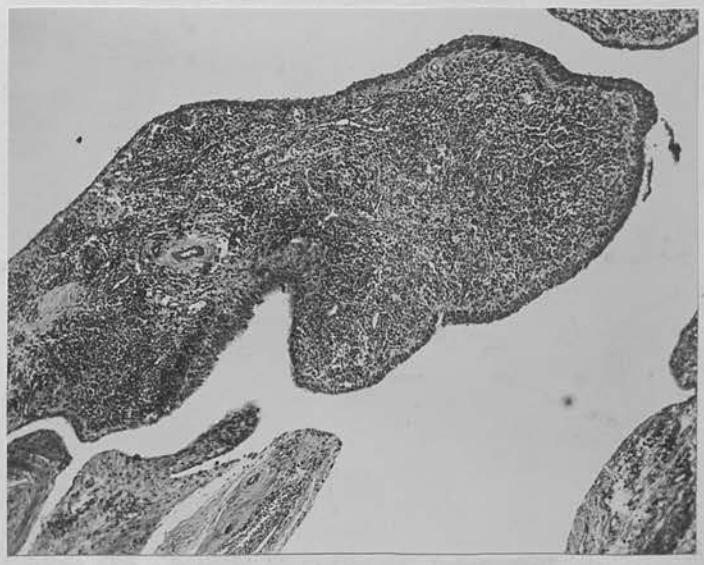

Fig.4. Case 5. Knee (lateral compartment) x 50. Large villous with hyperplastic surface layer, massive infiltration with lymphocytes, many capillaries. Adjacent villi show perivascular fibrosis.

Synovial Tissue in Rheumatoid Arthritis.

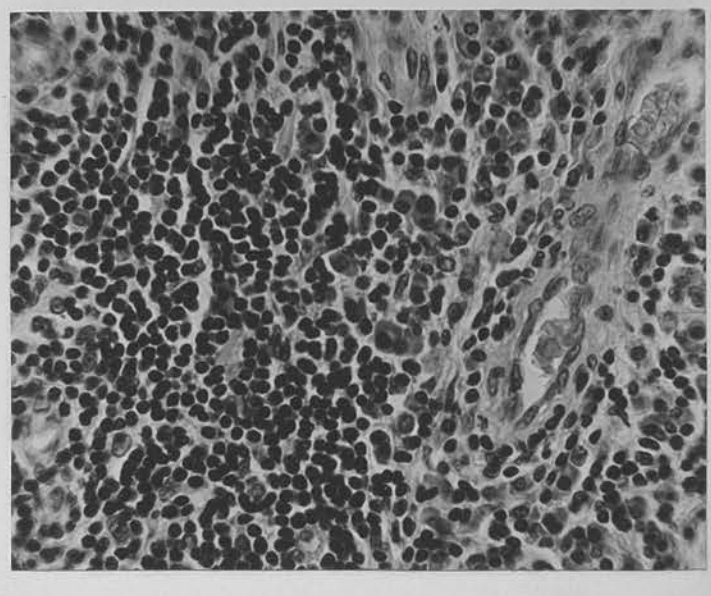

Fig. 5. Case 23. Left knee (suprapatellar) x 400.
High power view to show cytology of cellular infiltration - lymphocytes, plasma cells and histiocytes. See also Figs. 1 and 2.

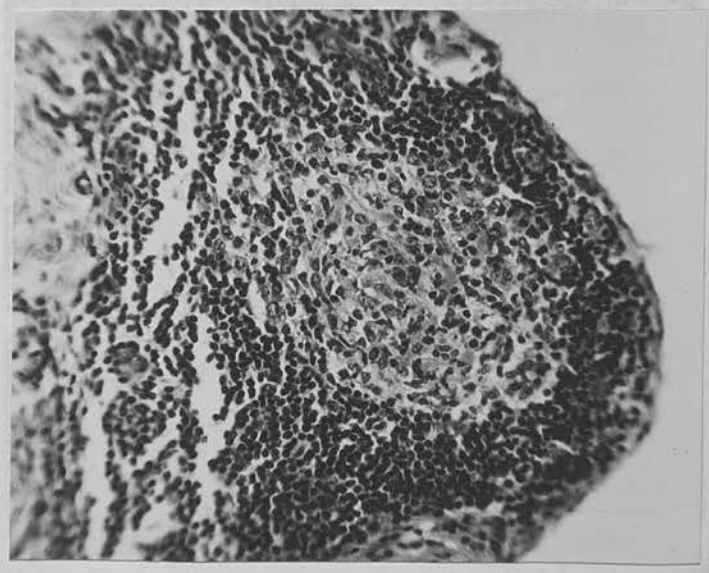

Fig. 6. Case 23. Left knee. x 250.
Another field from same section as Fig. 5, showing lymphocytic focus with germinal centre.

Synovial Tissue in Rheumatoid Arthritis.

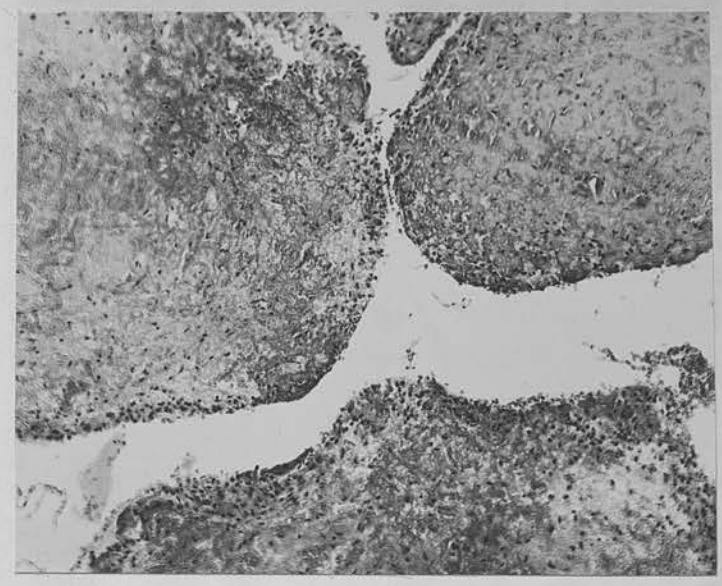

Fig. 7. Case 39. Elbow. x 100.
Necrosis of three large villi which have been infiltrated with round cells. See also Fig. 3.

Fig. 8. Case 21. Knee (medial compartment) x 100.
Massive round cell infiltration of deeper part of synovial tissue with extensive necrosis (centre).

Table IV.

Synovial Tissue from Joints in Rheumatoid Arthritis showing Histological Evidence of Activity but lacking all " Diagnostic " Features.

Case No.	Joint	Total Duration	Affected Joint			Histological Features						
			Duration	Stage	Clinical Activity	a	b	c	d	e	f	g
1	shoulder	9 yrs.	?	III	Active			+		+	+	
2	shoulder	10 yrs.	? 10 yrs	IV	Inactive		+			+	+	+
3	Knee	10 yrs.	> 8 yrs	IV	"			sm	+	+		
7	knee	?	< 2 yrs	II	Active	+		+	+	+		+
8	knee	8 yrs	4 yrs	IV	Inactive	+	+		+	+	+	
9	elbow	> 8 yrs	?	II	Active	+		+	+	+	+	
11	knee	2 yrs	< 2 yrs	I	"			sm		+			*
12	knee	32 yrs	< 30 yrs	?	?	+			+	+	+	+
13	shoulder	5 yrs	?	II	Active			sm		+	+	+
	knee		5 yrs	III	"			sm		+	+	
14	shoulder	6 yrs	?	II	Inactive	+	+		+	+	+	+ (met)
18	prox. inter-phalangeal 3rd. R	$2\frac{1}{2}$ yrs	$2\frac{1}{2}$ yrs	I	Active		+	+	+	+	+	
	3rd. L						+	+	+	+		
20	knee	2 mths	2 mths.	I	"					+			†
21	knee	1 yr	< 1 yr	II	"	+		+	+	+	+	
22	prox. inter-phalangeal	12 yrs	12 yrs	II	"	+		+	+	+		
	knee		<12 yrs	?	?		+	+	+	+		
23	R knee	8 yrs	1 yr	II	Active		+	+	+	+	+	+
25	shoulder	$1\frac{1}{2}$ yrs	?	I	?	+	+		+	+	+	
	metacarpophalangeal		?	II	Active	+			+	+		+
	knee		?	?	"	+	+		+	+	+	
27	metacarpophalangeal	many yrs	?	III	Inactive	+				+	+	+
	prox. inter-phalangeal		?	?	"	+				+	+	+
28	metacarpophalangeal	21 yrs	?	IV	?	+		diff	+	+	+	
33	knee	?	?	?	?		+			+	+		†
37	knee	3 yrs	3 yrs	?	?	+		+	+	+	+	
40	prox. inter-phalangeal	many yrs.	?	II	?	+		+	+	+	+	
43	knee	1 yr	1 yr	I	Active		+			+	+		*
50	knee	7 yrs	3 yrs	II	"		+	+	+	+	+	+
56	knee	5 yrs	?	?	?	+	+			+		

Key to Histological Features.

a = hyperplasia of cells lining surface
b = increase in number and size of villi
c = massive lymphocytic and plasma cell infiltration with large foci
d = congestion and oedema
e = absence of specific features, e.g., tubercles
f = necrosis
g = fibrosis
met = metaplasia to cartilage
sm = foci of lymphocytes and plasma cells present but small.
* = appearances of non-specific granulation tissue in places
† = lesions present of similar structure to subcutaneous nodule
diff = massive lymphocytic and plasma cell infiltration without foci
● = healed arteritis
o = plasma cells unusually numerous.

Synovial Tissue in Rheumatoid Arthritis.

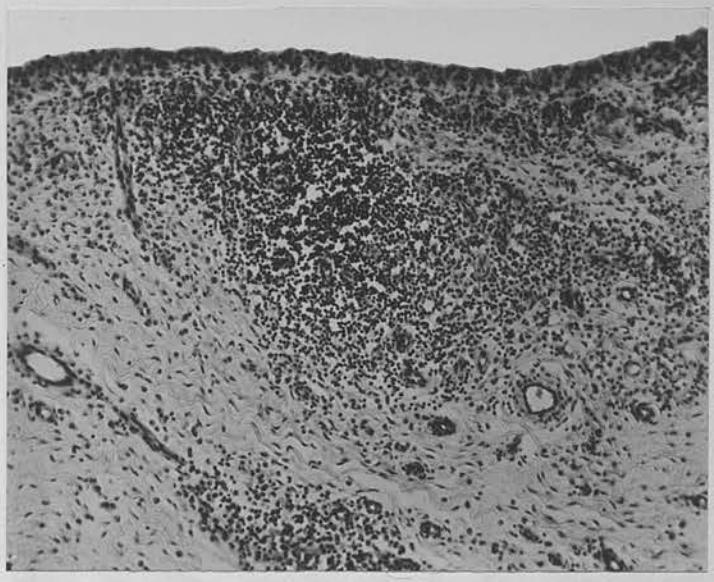

Fig. 11. Case 56. Knee (lateral compartment) x 100. Villous hypertrophy was absent in this case, but the other features - hyperplasia of lining cells, massive round cell infiltration, many capillaries and oedema are seen.

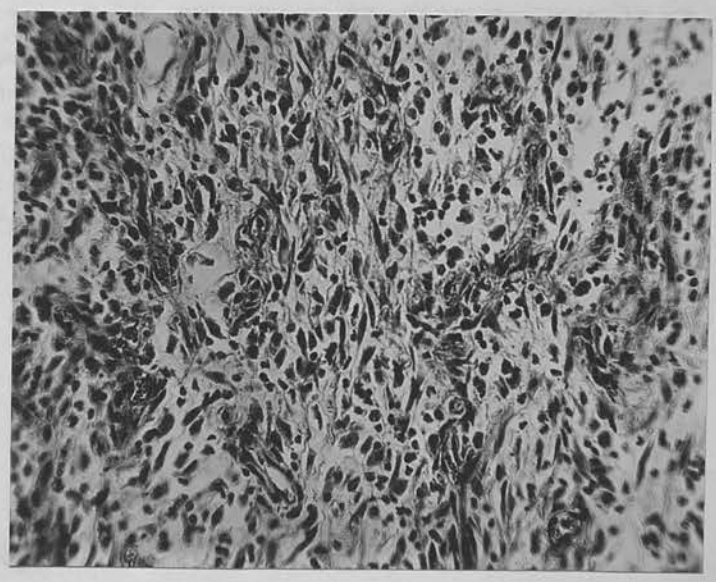

Fig. 12. Case 23. Right knee (suprapatellar) x 250. Unusually active fibroblastic proliferation accompanies round cell infiltration.

Synovial Tissue in Rheumatoid Arthritis.

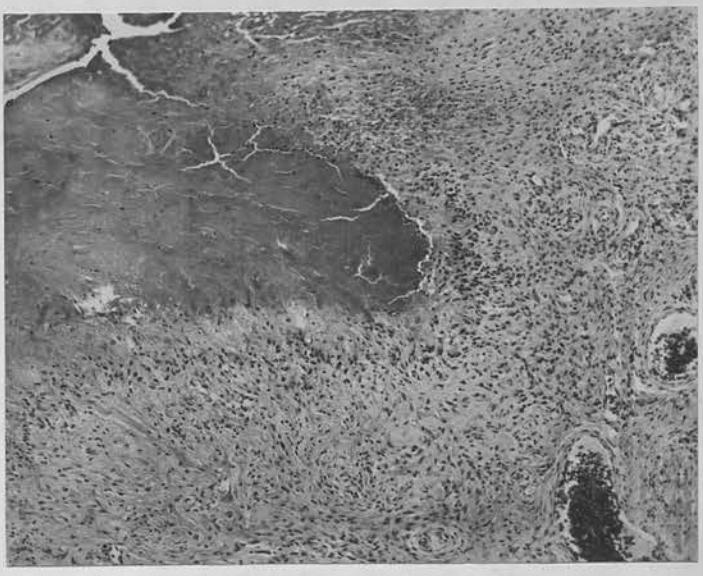

Fig. 13. Case 20. Knee (Medial to patella) x 75. Lesion of same type as subcutaneous nodule but in synovial tissue. Central necrotic area is surrounded by zone of fibroblasts in radial arrangement. Outer zone of cellular fibrous tissue infiltrated with round cells and containing large congested capillaries.

Synovial Tissue from Joints in Rheumatoid Arthritis showing Old-standing Fibrosis as the Predominant Histological Feature.

Case No.	Joint	Total Duration	Affected Joint			Histological features in addition to Fibrosis					
			Duration	Stage	Clinical Activity	a	b	c	d	e	f
1	Knee	9 yrs.	?	IV	Inactive			sm		+	
2	Knee	10 yrs.	? 10 yrs.	IV	"			sm		+	+
4	shoulder	10-12 y.	?	?	"		+			+	
8	elbow	8 yrs.	4-8 yrs.	IV	"					+	
14	knee	> 6 yrs.	$5\frac{1}{2}$ yrs.	II	"					+	
16	knee	?	?	?	?					+	
24	knee	4 yrs.	< 4 yrs.	?	Inactive	+	+			+	
26	knee	?	?	II	"					+	
27	knee	many yrs.	?	?	"	+	+			+	
31	shoulder	?	?	?	?		+			+	
35	knee	10 yrs.	10 yrs.	II	?						
40	distal inter phalangeal	many yrs.	?	III	?	+				+	
41	knee	5 yrs.	? 5 yrs.	II	Inactive					+	
42	knee	20 yrs.	?	?	?	+			+	+	
46	prox. inter phalangeal	2 yrs.	18 mths.	II	Inactive		+			+	
47	knee	5 yrs.	8 mths.	II	"	+			+	+	
48	metacarpo-phalangeal.	? 5 yrs.	? < 1 yr.	III	"					+	
	prox. inter-phalangeal									+	+
51	knee	4 yrs.	? 4 yrs.	III	"						+ met
53	knee	15 yrs.	$3\frac{1}{2}$ yrs.	IV	Active			sm			
54	knee	3 yrs.	1-2 yrs.	IV	Inactive						
57	knee	6 yrs.	?	?	?						
58	knee	3 yrs.	?	?	?						
59	knee	17 yrs.	?	?	?			sm			

Key to Histological Features - See Table IV.

plasia to cartilage. In six joints no abnormality was seen.

The lesions in one case of juvenile rheumatoid arthritis (Case 15, Fig. 14) and in one of "Felty's Syndrome" (Case 19, Fig. 15) differed in no way from those of typical adult rheumatoid arthritis. In another case of juvenile rheumatoid arthritis the synovial tissue showed patchy hyperplasia of the surface cells, oedema, diffuse round cell infiltration with occasional large foci and fibrosis. (Case 43, Fig. 16). In the only joint examined from rheumatoid arthritis with psoriasis, the appearances were healthy (Case 10).

The relationship between the histopathological features in the three groups of cases of rheumatoid arthritis showing histological abnormalities (including juvenile rheumatoid arthritis and " Felty's Syndrome) and the duration, stage and clinical activity in the affected joint is shown in Tables VI - VIII.

Ankylosing Spondylitis.

The range of lesions seen in ankylosing spondylitis was the same as that in rheumatoid arthritis (Table IX). The complete combination of lesions was seen in both hips of one patient (Case 197, Figs. 17-20). Two other joints showed evidence of activity in the form of villous and surface hyperplasia, together with patchy necrosis and congestion (Cases 199 & 203). In a further two, fairly marked fibrosis was associated with scattered large/

Synovial Tissue in Juvenile Rheumatoid Arthritis.

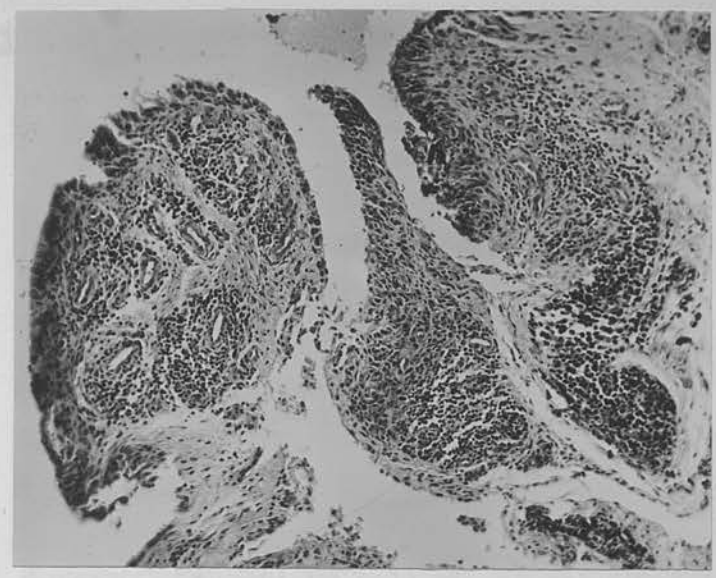

Fig.14. Case 15. Elbow x 100. The same features are seen as in adult rheumatoid arthritis - villous hyperplasia, hyperplasia of surface cells, oedema, vascularity and marked round cell infiltration.

Synovial Tissue in " Felty's Syndrome."

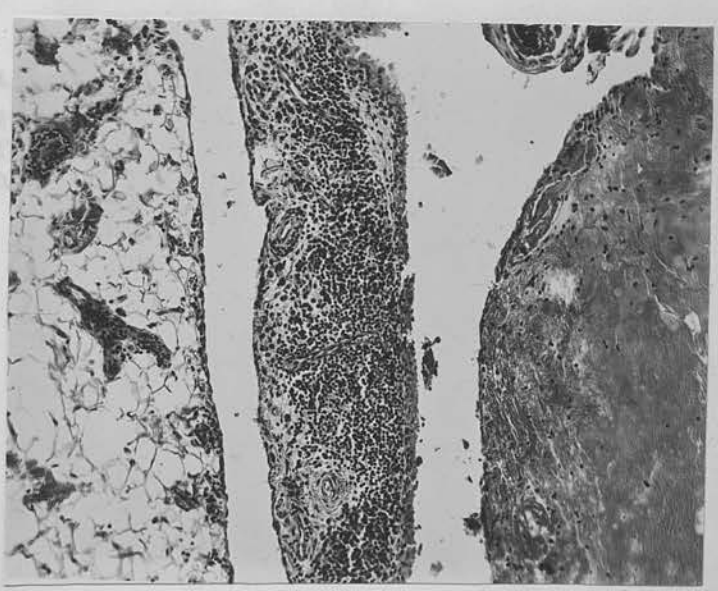

Fig.15. Case 19. Knee (fat pad) x 100. All the features of " typical " rheumatoid arthritis are seen - villous hyperplasia, slight hyperplasia of lining cells, vascularity and massive round cell infiltration (central villus) and necrosis (right).

Synovial Tissue in Juvenile Rheumatoid Arthritis.

Fig. 16. Case 43. Knee (lateral compartment) x 120.
Oedematous inflammatory tissue with necrosis of surface cells. Appearances elsewhere in this joint were more " characteristic."

Table VI.

Relationship of Duration of Rheumatoid Arthritis in Joints to Histological Features in Synovial Tissue.

Histology	Total	Duration							
		< 1 yr.		1-2 yrs.		2 -5 yrs.		> 5 yrs.	
		No.	%	No.	%	No.	%	No.	%
All "diagnostic" features present	14	2	14	8	57	2	14	2	14
Some evidence of activity	17	3	18	3	18	6	35	5	29
Fibrosis predominant	13	3	23	2	15	4	31	4	31
Total	44	8	18	13	30	12	27	11	25

28.

Table VII.

Relationship of Stage of Rheumatoid Arthritis in Joints to Histological Features in Synovial Tissue.

Histology	Total	Stage							
		I		II		III		IV	
		No.	%	No.	%	No.	%	No.	%
All " diagnostic " features present	13	1	8	10	77	2	15	0	0
Some evidence of activity	23	7	30	9	39	3	13	4	17
Fibrosis predominant	15	0	0	6	40	4	27	5	33
Total	51	8	16	25	49	9	18	9	18

29.

Table VIII.

Relationship of Clinical Activity of Rheumatoid Arthritis in Joints to Histological Features in Synovial Tissue.

Histology.	Total	Cases Clinically Active.	
		No.	%
All " diagnostic " features present	19	16	84
Some evidence of activity	23	16	30
Fibrosis predominant	16	1	6
Total	58	33	57

30.

Table IX.

Histological Features of Synovial Tissue from Joints in Ankylosing Spondylitis.

Case No.	Joint	Total Duration	Affected Joint			Histological Features						
			Duration	Stage	Clinical Activity	a	b	c	d	e	f	g
196	Hip	?	?	? II	?					+	+	
197	R. Hip	12 yrs.	? 12 yrs	III-IV	Active	+	+	+	+	+		
	L. Hip					+	+	+	+	+	+	fine
198	R. Hip	14 yrs.	?	IV	Inactive					+	+	
	L. Hip									+	+	
199	R. knee	7 yrs.	< 7 yrs	II	Inactive	+			+	+	+	+
	L. knee			IV						+	+	
200	Hip	18 yrs.	?	IV	Inactive			sm		+	+	
201	Sterno-clavicular	4 yrs.	5 mths.	II	Active	+	+			+	+	+
202	knee	12 yrs.	< 12 yrs.	IV	Inactive			+		+	+	+
203	Hip	?	?	?	?	+	+	sm	+	+	+	+

Key to Histological Features - See Table IV, p. 21.

Synovial Tissue in Ankylosing Spondylitis.

Fig. 17. Case 197. Left hip. x 35. Villous hyperplasia, slight proliferation and patchy necrosis of surface cells (left), focal infiltration with round cells, congestion and oedema.

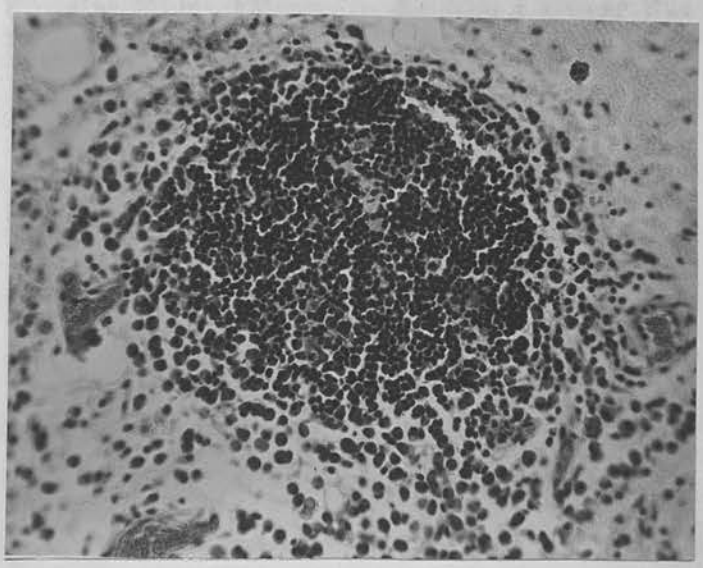

Fig. 18. Case 197. x 250. Another field from same section as Fig. 17, showing a single focus of lymphocytes and peripheral plasma cells. See also Figs. 19 and 20.

Synovial Tissue in Ankylosing Spondylitis.

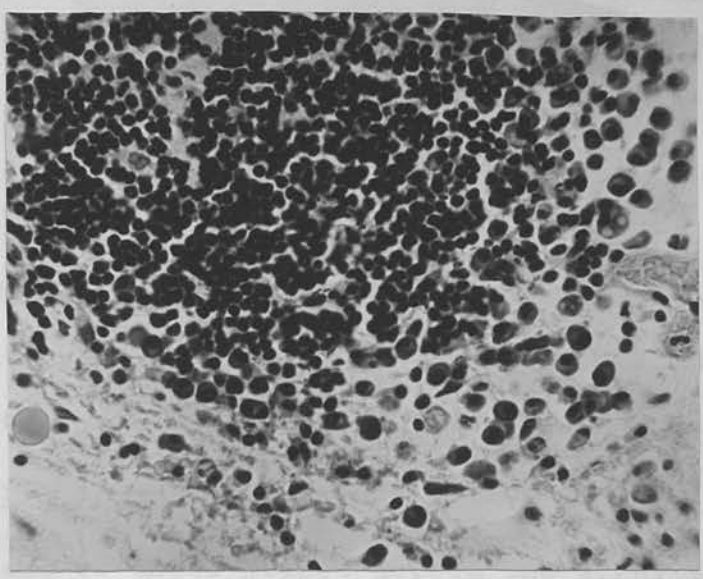

Fig. 19. Case 197. x 450. Higher power view of edge of focus in Fig. 18. Note Russell bodies in several plasma cells. See also Fig.20.

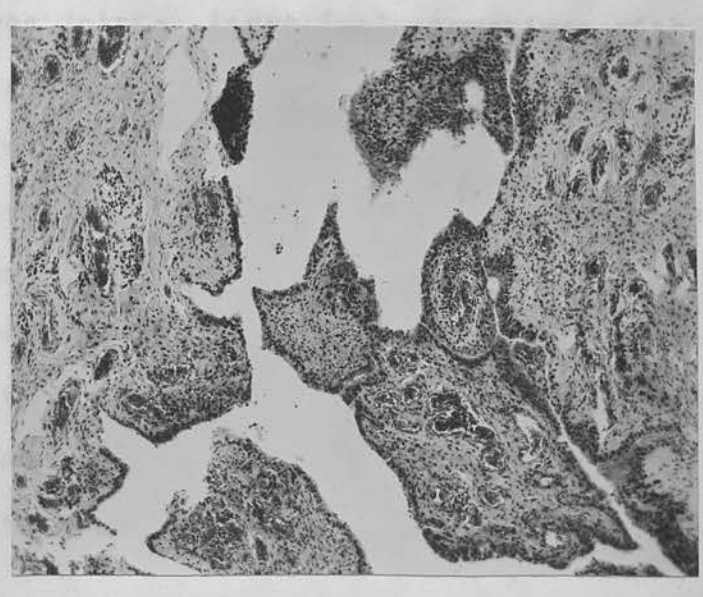

Fig. 20. Case 197. Right hip. x 50. Increase in number of villi, hyperplasia of surface layer with multinucleate cells (centre), oedema and marked congestion. Round cell infiltration is slight. Fibrosis beneath surface. (See also Figs. 17 to 19).

large foci of lymphocytes (Case 202, Fig. 21) or a little patchy necrosis (Case 201, Fig. 22). Fibrosis was the main feature in the remaining five joints, sometimes with a few small foci and slight villous or surface hyperplasia. The duration, stage and activity in the affected joints is also recorded in Table XI. There are too few cases to permit analysis of these features in relation to the histology.

Osteoarthritis.

Most of these joints showed the synovial lesions which are regarded as characteristic of osteoarthritis, namely fibrosis, sometimes with villous hyperplasia, with or without surface hyperplasia and minimal round cell infiltration (Fig. 23). In three joints, large foci, sometimes with germinal centres were seen along with a good deal of diffuse infiltration (Fig. 24). These features were accompanied by marked fibrosis in two of the cases, whereas in the third fibrosis was absent so that the features were identical with those of rheumatoid arthritis (Case 234, Fig. 25). This was a case of pure osteoarthritis of the mid-tarsal joint, associated with flat feet and hallux rigidus.

Gout.

Typical urate deposits were seen in all five joints and were present only in this disease (Fig. 26). Other lesions seen in one case (Case 243) were villous hyperplasia associated with diffuse round cell infiltration and small patches of necrosis/

Synovial Tissue in Ankylosing Spondylitis.

Fig. 21. Case 202. Knee (suprapatellar) x 50. Marked fibrosis of synovial tissue with large focus of lymphocytes.

Fig. 22. Case 201. Sternoclavicular Joint. x 85. Slight villous hyperplasia with marked fibrosis and many capillaries. Necrosis of surface (top).

Synovial Tissue in Osteoarthritis.

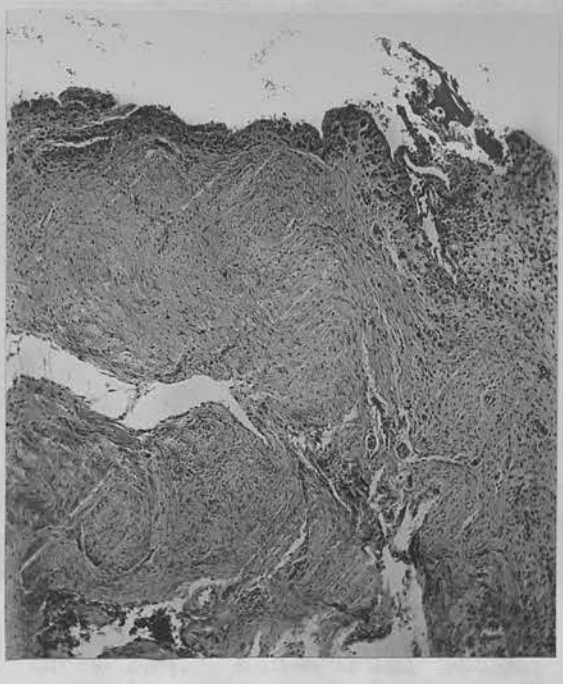

Fig. 23. Case 212. Hip. x 50. Focal hyperplasia of lining cells (top) and marked fibrosis of rest of tissue. Minimal round cell infiltration (top right).

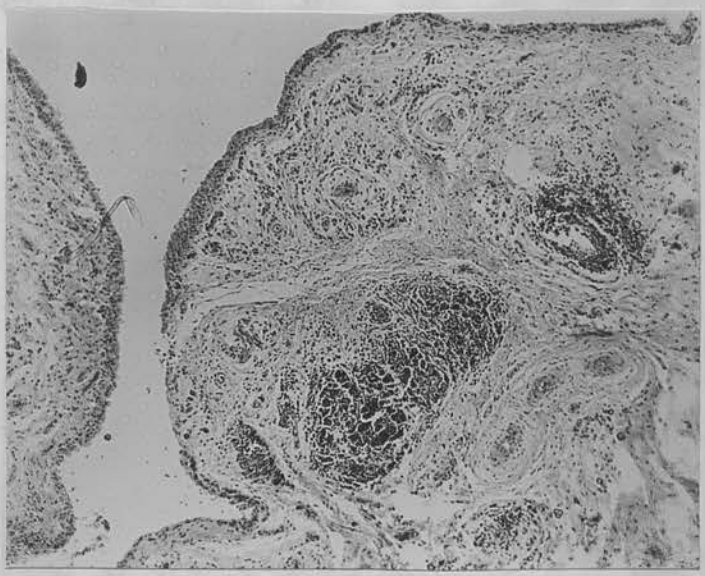

Fig. 24. Case 214. Hip. x 50. Focal hyperplasia of lining cells, oedema and fibrosis of underlying tissue. Round cell infiltration with prominent foci of lymphocytes.

Synovial Tissue in Osteoarthritis.

Fig. 25. Case 234. Mid-tarsal Joint. x 100. Oedema, congestion and marked round cell infiltration. Villous hyperplasia and thickening of surface layer were seen elsewhere.

Synovial Tissue in Gout.

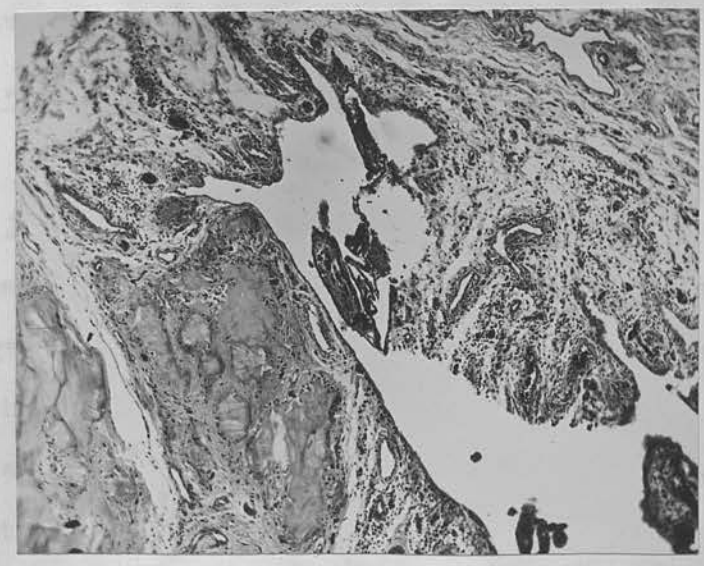

Fig. 26. Case 244. Wrist. x 50. Urate deposits with surrounding histiocytic reaction (left). Villous hyperplasia, oedema, congestion and diffuse round cell infiltration elsewhere.

necrosis (Fig. 27) and villous hyperplasia associated with well-developed fibrosis (Fig. 28).

Rheumatic Fever.

The appearances in three of the joints were normal. Mild lesions were seen in four joints and consisted of congestion, slight thickening of the surface layer, minimal round cell infiltration and occasional patches of necrosis of the surface (Figs. 29 & 30). More marked changes, including patches of necrosis in the deeper tissue, or slight villous hyperplasia, both with round cell response were seen in four joints. In one section from this group, the necrosis and round cell infiltration were focal in character, (Case 249, Fig. 31). Slight to moderate fibrosis was seen in two of the joints (Fig. 32).

Systemic Lupus Erythematosus.

A wide range of appearances was seen here. One joint was normal. The mildest abnormality resembled that seen in rheumatic fever, namely, congestion, mild lymphocytic infiltration and patchy surface necrosis (Figs. 33 & 34). More marked changes were seen in a metacarpo-phalangeal joint, where there was villous hyperplasia, slight surface thickening and more pronounced round cell infiltration (Case 526, Fig. 35), the appearances bearing a distinct resemblance to those of rheumatoid arthritis (Case 40, Fig. 36). The most severe lesions were necrotising arteritis

and/

Synovial Tissue in Gout.

Fig. 27. Case 243. Knee (lateral compartment) x100
Small urate deposits (bottom right) but main feature is round cell infiltration. Other features are necrosis (top right) and metaplasia to cartilage (bottom left). See also Fig. 28.

Fig. 28. Case 243. Another section from the same joint as Fig. 27, showing villous hyperplasia and marked fibrosis. x 75.

Synovial Tissue in Rheumatic Fever.

Fig. 29. Case 248. Knee (suprapatellar) x 90. Necrosis of superficial tissue (centre). Slight oedema and minimal round cell infiltration beneath surface.

Fig. 30. Case 249. Knee (medial compartment) x 100. Congestion, oedema and round cell infiltration just beneath surface. See also Figs. 31 and 32.

Synovial Tissue in Rheumatic Fever.

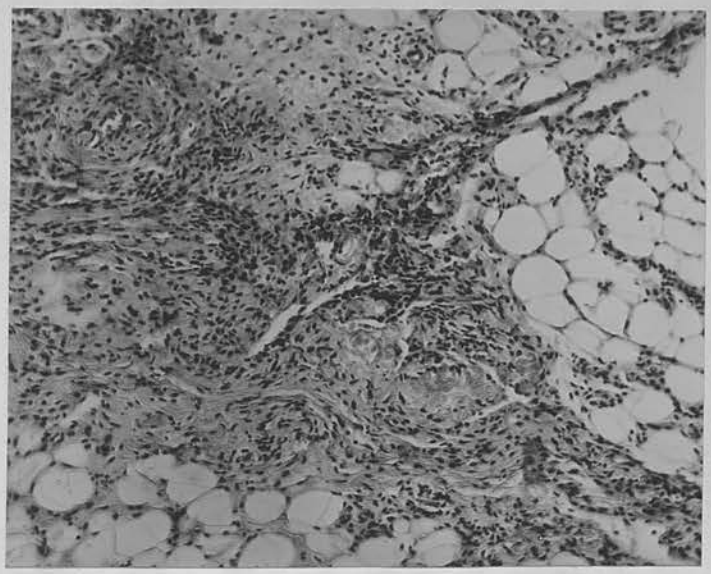

Fig. 31. Case 249. Knee (fat pad). x 100. Focal lymphocyte and histiocyte infiltration associated with swelling and fragmentation of collagen (centre right). See also Figs. 30 and 32.

Fig. 32. Case 249. x 100. Another field from same section as Fig. 31, showing congestion and slight round cell infiltration with superimposed fibrosis. See also Fig. 30.

Synovial Tissue in Systemic Lupus Erythematosus.

Fig. 33. Case 524. Knee (medial compartment) x 100. Fine villi showing mild lymphocytic infiltration and patchy necrosis (above centre and left).

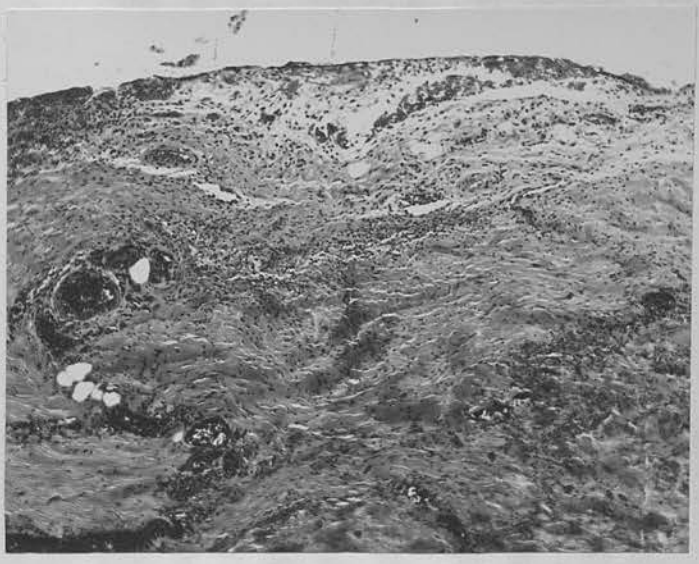

Fig. 34. Case 523. Knee (lateral compartment) x 60. Oedema and necrosis of superficial zone with lymphocytic reaction and congestion in deeper tissue. See also Fig. 37.

Comparison of Synovial Tissue in Systemic Lupus Erythematosus and Rheumatoid Arthritis.

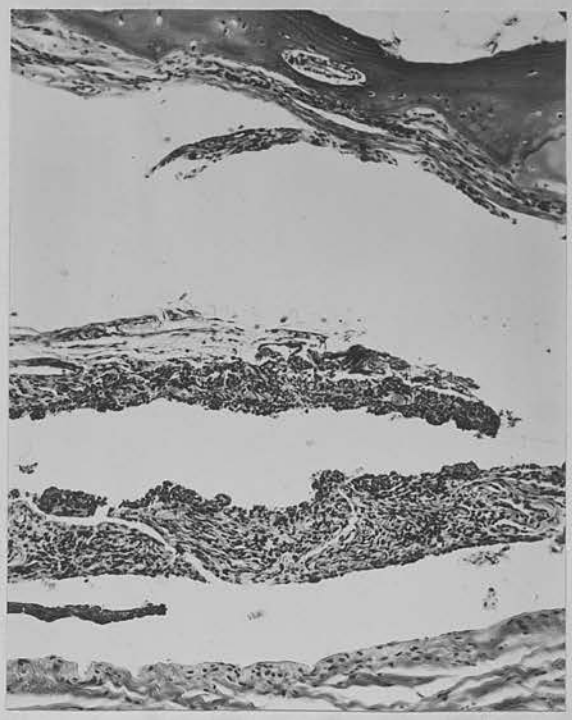

Fig. 35. Case 526. (lupus) Metacarpophalangeal Joint. x 100. Villous hyperplasia, slight thickening of surface layer (centre, right) and round cell infiltration. Note thin layer of granulation tissue (" pannus ") on surface of bone (top).

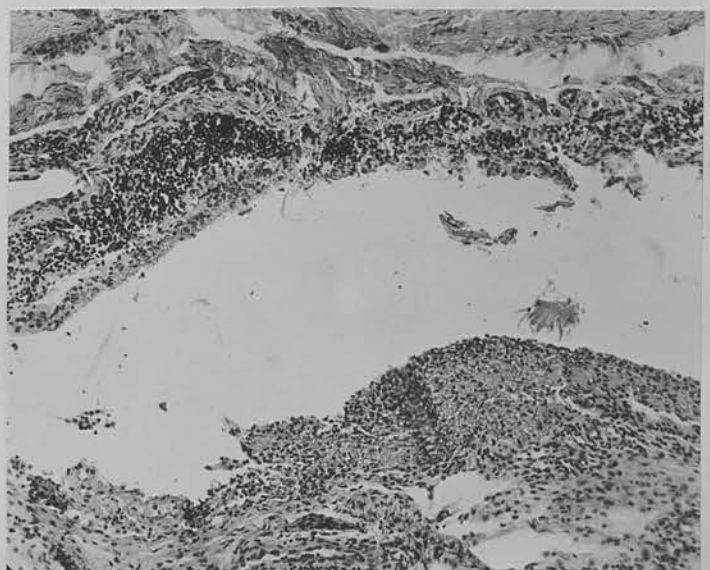

Fig. 36. Case 40 (rheumatoid). Metacarpophalangeal Joint. x 100. Round cell infiltration is more intense ; erosion of bone was present nearby.

and massive infiltration of adjacent tissue with polymorphs and lymphocytes (Case 523, Fig. 37), the lesions resembling closely those of polyarteritis nodosa.

Polyarteritis Nodosa.

No evidence of acute polyarteritis was seen, two of the cases showing normal synovial tissue. Patchy healed lesions, affecting both arteries and veins were seen in the third case together with capillary thrombosis and slight fibrosis (Case 542, Fig. 38).

Non-specific Synovitis.

This group includes cases of recurrent monarticular synovitis of unknown aetiology with no history or clinical evidence of rheumatic disease elsewhere, so-called " villous arthritis " of the knee and synovitis following trauma. In most of the cases, the disease was confined to the synovial tissue, with minimal involvement of other joint structures.

The histopathology of most of these cases differed considerably from rheumatoid arthritis in that hypertrophy of the synovial tissue was slight and the inflammatory infiltration wholly diffuse or with only scanty small foci. However, 9 of the joints showed all the lesions seen in rheumatoid arthritis with patchy necrosis as well in two of them. Many plasma cells were noted in 2 cases (Table X). A further two showed appearances closely resembling those of rheumatoid arthritis, but/

Synovial Tissue in Systemic Lupus Erythematosus.

Fig. 37. Case 523. Knee. x 100. Block from some region on Fig. 34. Normal wall of small artery (top right) becomes necrotic at arrows and the lumen is thrombosed. Intense acute inflammation of adjacent tissue.

Synovial Tissue in Polyarteritis Nodosa.

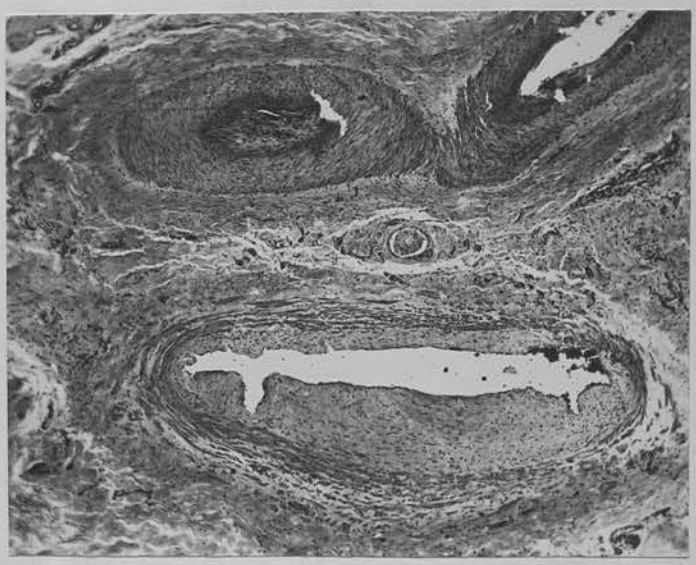

Fig. 38. Case 542. Knee (fat pad) x 85. An artery (above) and vein (below) showing marked intimal fibrosis with loss of elastic tissue. Suggestion of recanalisation of artery. (Similar lesions present in other tissues).

Table X.

Histological Features of Synovial Tissue from Joints in Cases of Non-specific Synovitis where Lesions resemble those of Rheumatoid Arthritis.

Case Number	Joint	Diagnosis	Duration	Histological Features						
				a	b	c	d	e	f	g
559	ankle	Synovitis	6 mths.	+	+	+	+	+		
563	knee	Post-traumatic synovitis	16 mths.	+	+	+	+	+		+
564	knee	Recurrent synovitis	2 mths,	+	+	diff.	+	+	+	
565	knee	Synovitis	?	+	+	+	+	+		
575	knee	Post-traumatic synovitis	2 yrs.	+	+	+	+	+		
578	knee	Recurrent synovitis	15 mths.	+	+	+	+	+		
580	knee	Synovitis	3½ yrs.	+	+	+	+	+		
585	knee	Synovitis	?	+	+	+	+	+		+
591	knee	Villous arthritis	7 mths.	+	+	diff.	+	+		+
592	knee	Synovitis	3 wks.	+	+	+	+	+		+
598	knee	Synovitis	8 mths.	+	+	+	+	+	+	

Key to Histological Features - See Table IV, p. 21.

but lacked the large follicles of round cells (Case 598, Fig. 39).

Loose Bodies in Joints.

In 6 of these cases the synovial lesions resembled those of osteoarthritis. In one the inflammatory lesions were the same as those of rheumatoid arthritis, though the hyperplasia was lacking (Case 600). Another showed marked hyperplasia and congestion and fibrosis without any inflammation (Case 604).

Septic Arthritis.

One case in this category showed all the features of rheumatoid arthritis except surface thickening : necrosis of patchy distribution was present (Case 610). This patient had a history of septic arthritis of the knee following a gun-shot wound 27 years previously. In a second case marked fibrosis was accompanied by inflammatory infiltration identical with that of rheumatoid arthritis: in this case the arthritis was of 10 years duration following a fractured patella (Case 606). The lesion in the remaining cases was non-specific granulation tissue.

Osteochondritis.

The appearances in all cases were like those of osteoarthritis.

Lesions of Menisci.

The synovial tissue in most cases of tears or detachment of menisci and intra-articular ligaments

was/

Synovial Tissue in Non-specific Synovitis.

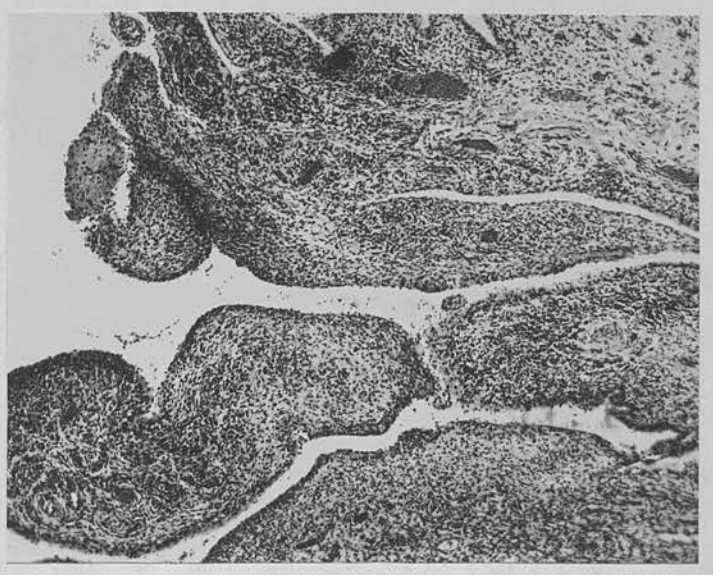

Fig. 39. Case 598. Knee (medial compartment) x 50. Villous hyperplasia, thickening of surface layer, oedema, congestion and massive round cell infiltration. Many of the cells are plasma cells.

was normal or showed mild subacute or chronic inflammation without hypertrophy. Occasionally fibrosis was seen together with moderate hypertrophy, the appearances resembling those of osteoarthritis (Case 635, Fig. 40). Four cases showed all the features of rheumatoid arthritis with necrosis in three. Large germinal follicles were a feature in three of these cases (Case 640, Fig. 41) and many plasma cells were seen in one of them (Case 622). Another case showed surface hyperplasia, congestion and round cell infiltration like rheumatoid arthritis, but no villous hyperplasia (Case 639). In a sixth only surface hyperplasia was lacking (Case 642) and in a seventh inflammation was less marked (Case 644) (Table XI).

The cases of cysts of meniscus showed comparatively little change in the synovial tissue. This was usually minimal round cell infiltration or fibrosis.

Haemophilia.

The appearances here were more or less characteristic, consisting of moderate surface thickening, variable diffuse round cell infiltration and fibrosis with gross haemosiderin deposition. Both cases showed only these old-standing lesions.

Tuberculous Arthritis.

All the 35 cases of tuberculous arthritis in which synovial tissue was available showed clear-cut evidence of the disease, although detailed search

Table XI.

Histological features of Synovial Tissue from Joints in Cases of Tears of Menisci where Lesions resemble those of Rheumatoid Arthritis.

Case No.	Duration	Histological Features.						
		a	b	c	d	e	f	g
620	1 yr.	+	+	+	+	+	+	
622	2 yrs.	+	+	+	+	+	+	
630	14 mths.	+	+	+	+	+		fine
639	3 mths.		+	sm	+	+		
640	?	+	+	+	+	+		
643	3 mths.	+		+	+	+	+	
644	4 wks.	+	+	sm	+	+		

Key to Histological Features - See Table IV, p. 21.

Synovial Tissue accompanying Tears of Menisci.

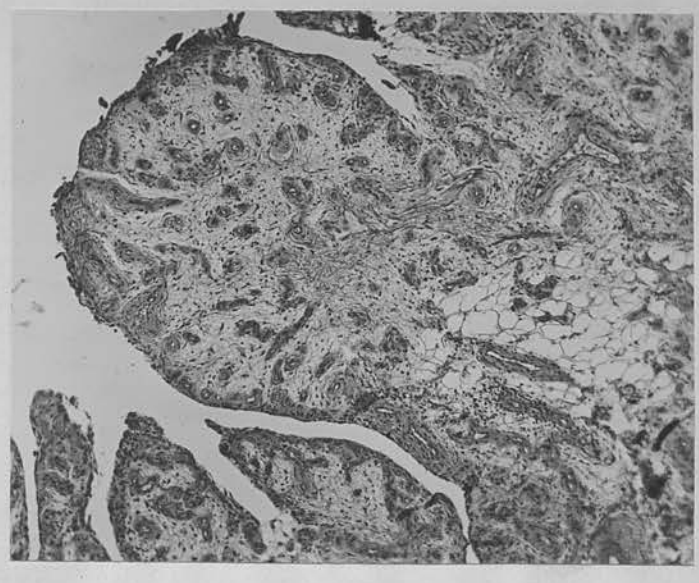

Fig. 40. Case 635. Knee (medial compartment) x 50. Features resembling osteoarthritis, i.e., villous hyperplasia with fibrosis. Minimal lymphocytic infiltration at one point (lower right).

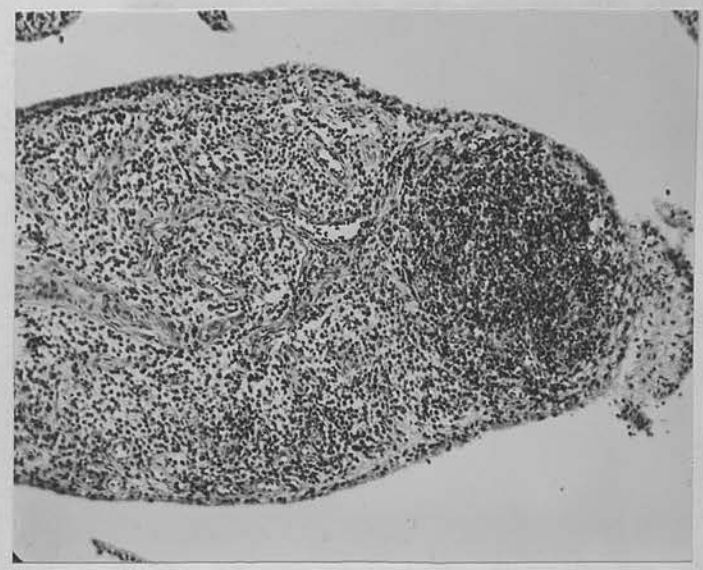

Fig. 41. Case 640. Knee (medial compartment) x 100. Single villus which was one of many showing features resembling rheumatoid arthritis. Compare with Figs. 1, 4, 14 and 15.

was necessary in some of them in order to demonstrate tubercles. In two cases where tubercles were plentiful, parts of the synovial tissue showed appearances just like those of rheumatoid arthritis (Cases 759 & 760, Fig. 42).

Syphilitic Arthritis.

In one case the appearances were those of subacute synovitis with marked fibrosis and occasional large foci of lymphocytes and plasma cells (Case 701). The second case resembled rheumatoid arthritis closely, though lacking hyperplasia of synovial cells. Capillaries were particularly plentiful and showed more marked swelling of endothelium than was noted in rheumatoid arthritis (Case 702, Fig. 43).

Amyloidosis.

One very interesting patient (Case 925) was encountered whose clinical features were indistinguishable from those of rheumatoid arthritis, with involvement of the shoulder, elbows, wrists, hands and knees. She died of renal failure due to chronic pyelonephritis. The only joint examined was the left knee which showed marked hyperplasia of the synovial tissue, much of which appeared necrotic (Fig. 44) but gave a positive iodine test (Fig. 45). Microscopical examination of the knee and several bursae in the neighbourhood showed very extensive amyloid deposition in the synovial tissue, but no inflammation (Figs. 46-48). Amyloid was

also/

Synovial Tissue in Tuberculous Arthritis.

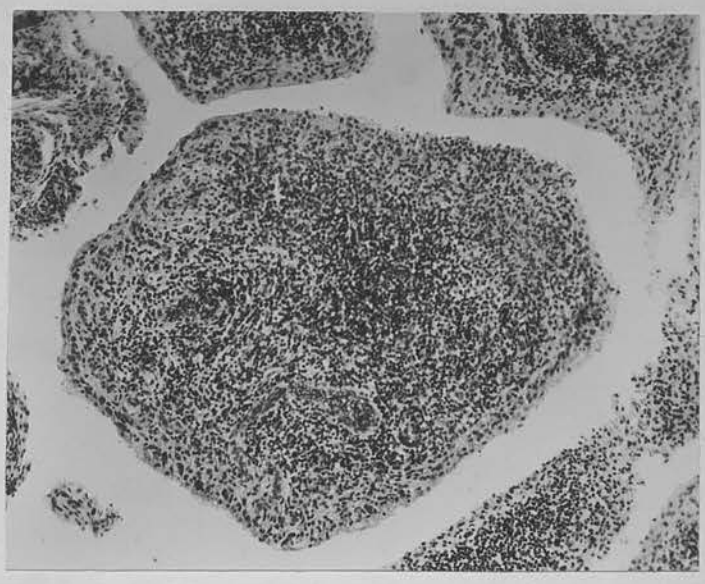

Fig. 42. Case 700. Knee (lateral compartment) x 100. Although tubercles were present in many places, much of the tissue showed features resembling rheumatoid arthritis. Compare with Fig. 4.

Synovial Tissue in Syphilitic Arthritis.

Fig. 43. Case 702. Knee. x 100. Villous hyperplasia, dense infiltration with lymphocytes and plasma cells and swelling of capillary endothelium.

Amyloidosis of Left Knee.

Fig. 44. Masses of friable synovial tissue infiltrated with amyloid are seen above and medial to the patellar surface of the femur and around the patella. Extensive degeneration of articular cartilage is seen. See also Figs. 45 - 48.

Amyloidosis of Left Knee.

Fig. 45. Same tissue as Fig. 44 after application of Lugol's iodine (much of the dark brown colour faded during the exposure of this photograph.

Amyloidosis of Synovial Tissue.

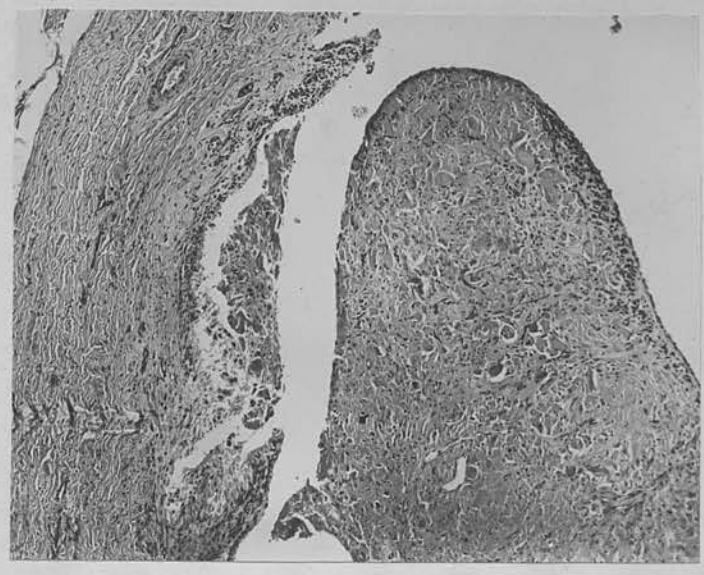

Fig. 46. Suprapatellar region of knee shown in Fig. 44. x 50. One large and one small villous process replaced by hyaline amyloid material which absorbed Congo red dye.

Fig. 47. x 50. Medial compartment of same knee showing excessive number of villi with thickening synovial layer due to mixture of oedema and amyloid. Slight lymphocytic reaction in places.

Amyloidosis of Synovial Tissue.

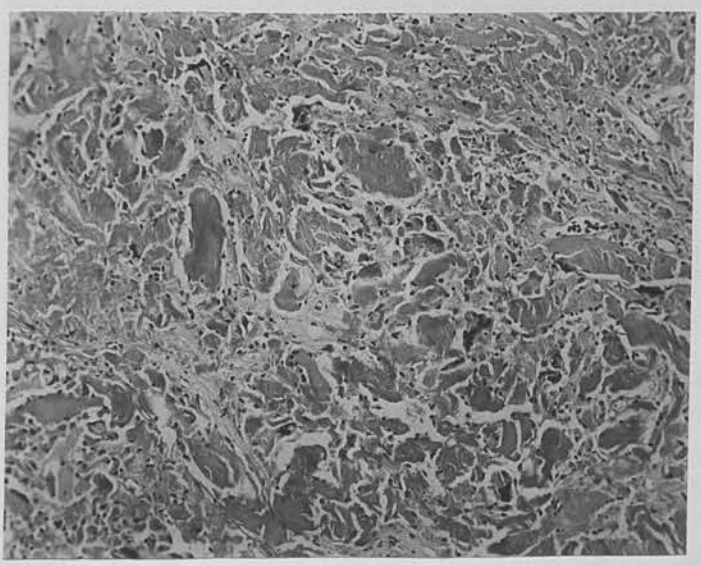

Fig. 48. x 50. Masses of amyloid and foreign-body giant cells within a bursa on posterior aspect of joint shown in Figs. 44 and 45.

also found in the tongue, diaphragm and deltoid, but not in any viscera.

B. Bursae.

Rheumatoid Arthritis.

None of the bursae showed all the features seen in the joints, though evidence of activity was seen in all but one (Table XII). Four of the bursae had arisen close to subcutaneous nodules and these lesions formed part of the wall (Figs. 49 & 50). In one of these cases most of the wall of the bursa showed marked hyperplasia of synovial cells with necrosis of segments of the surface and diffuse round cell infiltration beneath the surface. Russell bodies were associated with some of the many plasma cells (Case 60, Fig. 51). Extensive necrosis of the bursa wall and adjacent muscle was a feature in another case and was accompanied by many foamy histiocytes (Case 1, Fig. 52).

Non-specific Bursitis.

The appearances in the majority of cases were those of mild to moderate non-specific inflammation with deposition of fibrin, formation of granulation tissue and proliferation of small vessels. Variable numbers of giant cells were seen in some specimens. None of the cases showed the subcutaneous nodule type of lesion, but in three all the features of rheumatoid synovitis were seen (Case 808, Fig.53).

Table XII.

Histological Features of Bursae in Rheumatoid Arthritis.

Case No.	Site	Histological Features.							
		a	b	c	d	e	f	g	other features
1	shoulder			+		+	+	+	many foam cells
24	prepatellar	+				+		+	
40	prepatellar	+	+		+	+	+		
	prepatellar	+		+	+	+	+		
60	elbow		+	diff.	+	+	+		subcutaneous nodule in wall
61	elbow								subcutaneous nodule in wall
62	R. elbow						+	+	focal cholesterol resembling
	L. elbow						+	+	old-standing nodule

Key to Histological Features - See Table IV, p. 21.

Synovial Tissue in Rheumatoid Arthritis.

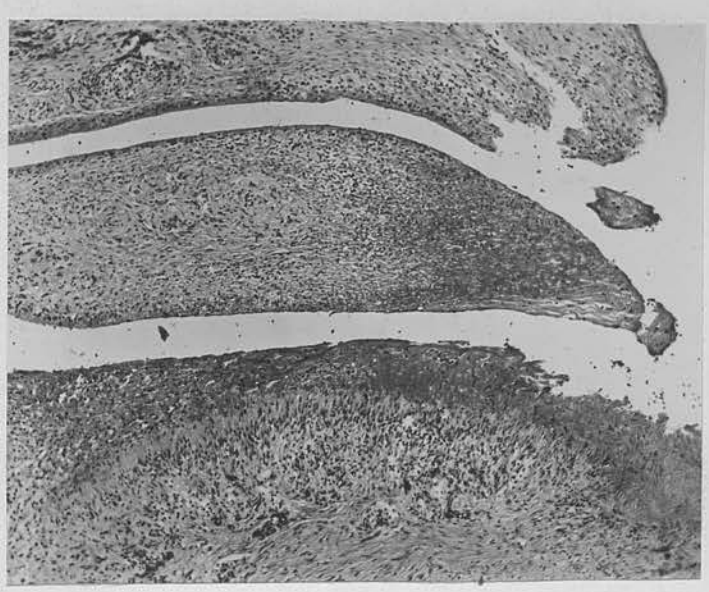

Fig. 49. Case 61. Bursa from elbow. x 50. Villous hyperplasia of wall. The upper two villi show surface hyperplasia, oedema, fibrosis and slight round cell infiltration, with necrosis at the tip of one. In the lower villus an inner zone of necrosis is separated from non-specific inflammation by a zone of fibroblasts showing palisade arrangement resembling the rheumatoid subcutaneous nodule. See Section III and Figs. 96-97, p. 135.

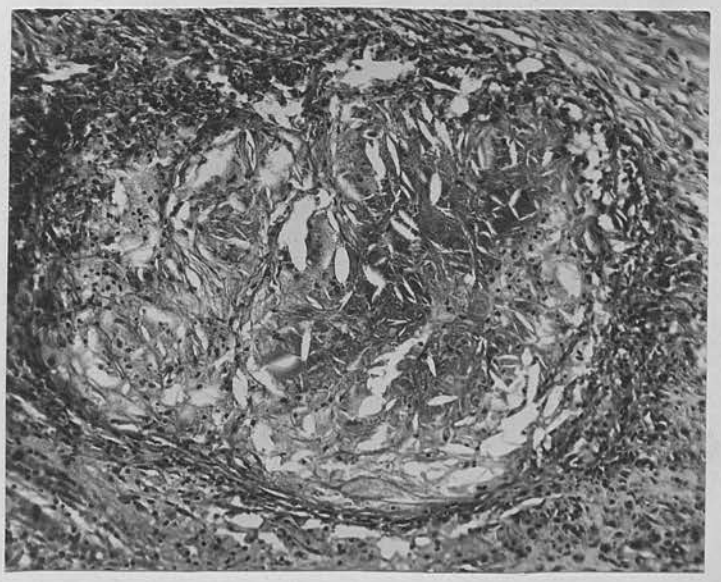

Fig. 50. Case 62. X 100. Bursa from right elbow. Collection of cholesterol clefts and foam cells in wall of bursa. See Figs. 96-98.

Synovial Tissue in Rheumatoid Arthritis.

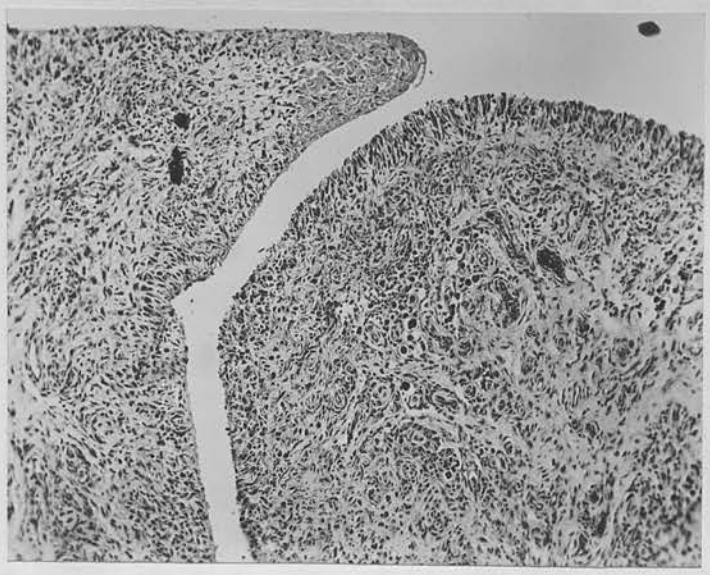

Fig. 51. Case 60. Bursa from elbow. x 100. Two large villi showing hyperplasia of surface layer, part of which is necrotic, congestion, oedema and round cell infiltration. The dark masses (centre) are plasma cells containing Russell bodies.

Fig. 52. Case 1. Bursa from shoulder region. x 100. Extensive central necrotic mass (above), intermediate zone of foamy histiocytes and outer zone of fibrous tissue infiltrated with many lymphocytes.

Table XIII.

Histological Features of Bursae where Lesions resemble those of Rheumatoid Arthritis.

Case Number	Site	Histological Features.						
		a	b	c	d	e	f	g
711	elbow	+	+	+	+	+	+	+
714	elbow	+	+	+	+	+		+
751	Prepatellar		+	diff.		+		+
756	wrist	+	+	+	+	+		+
808	Baker's cyst			diff.		+		
				diff.		+		
		+	+	+	+	+		
		+	+	+	+	+		

Key to Histological Features - See Table IV, p. 21.

Synovial Tissue in Non-specific Bursitis.

Fig. 53. Case 808. Semimembranosus bursa. x 100. Villi showing hyperplasia of lining cells, congestion, oedema and marked focal round cell infiltration.

In a fourth case, hyperplasia was slight with marked focal and diffuse round cell infiltration (Case 756) and in a fifth there was hyperplasia of synovial cells, fibrosis and small foci alternating with heavy diffuse infiltration with round cells (Case 751) (Table XIII).

Tuberculous Bursitis.

All these cases were clearly tuberculous, with no evidence of lesions comparable with those of rheumatoid arthritis.

C. Tendon Sheaths.

In three of the cases of rheumatoid arthritis the appearances were identical with those in the joints, all the features being present (Figs. 54 & 55). Round cell infiltration was less intense in the fourth case (Case 66, Fig. 56), but all the other features were seen. Polymorphs were present in large numbers in one case (Case 66).

Systemic Lupus Erythematosus.

The tendon sheath lesions in this disease were more florid than the joint lesions in the same cases, but had passed unnoticed clinically. Considerable villous hyperplasia was present together with patchy thickening of the surface layer and moderate, usually diffuse, round cell infiltration. The most striking lesion, however, was swelling, necrosis and fragmentation of collagen (Figs. 57 & 58). In one section, a large focus/

Synovial Tissue in Rheumatoid Arthritis.

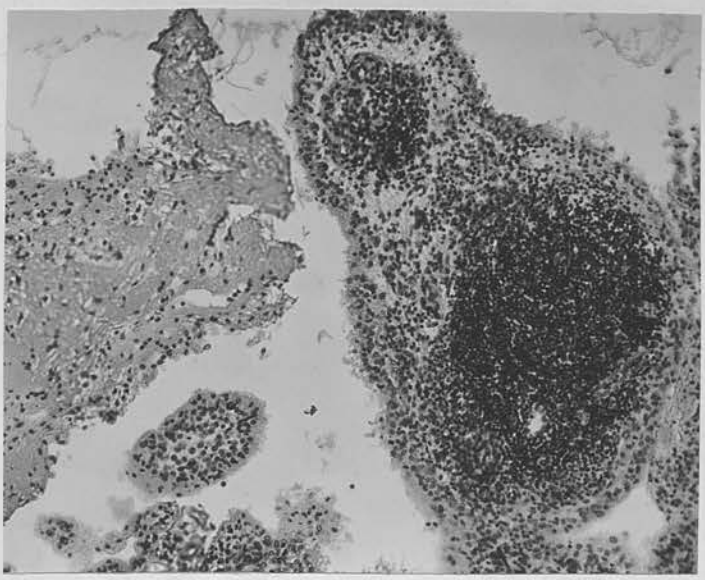

Fig. 54. Case 65. Tendon sheath from wrist. x 100. Villous hyperplasia, thickening of surface layer, oedema, massive lymphocytic infiltration and necrosis are all seen.

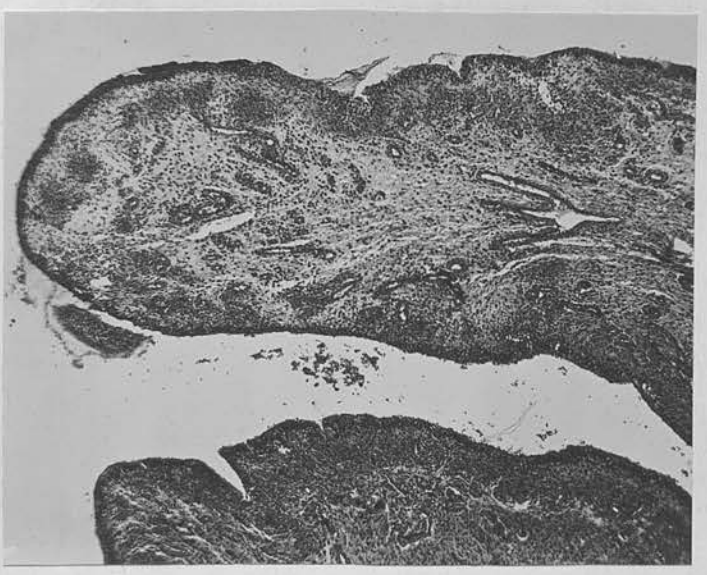

Fig. 55. Case 63. Tendon sheath from wrist. x 35. All features of rheumatoid arthritis are seen. In this case tenosynovitis preceded arthritis by several months.

Synovial Tissue in Rheumatoid Arthritis.

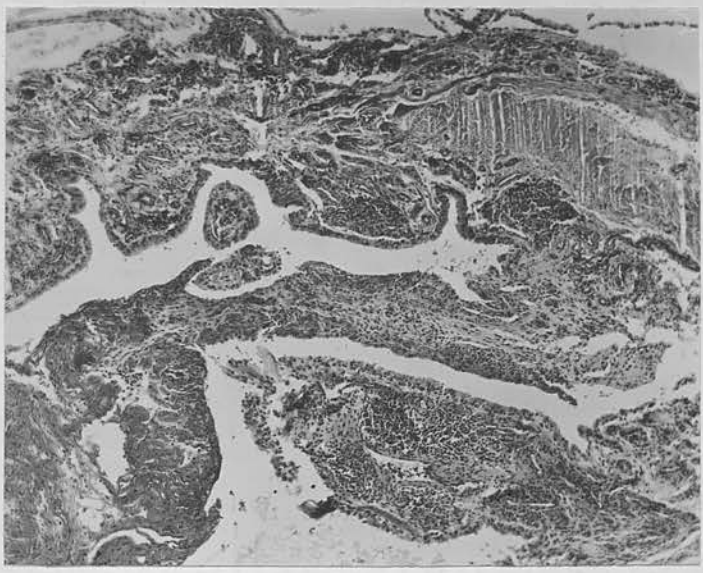

Fig. 56. Case 66. Tendon sheath from finger. x 50. Another example showing fibrosis as well as active inflammation and necrosis.

Synovial Tissue in Systemic Lupus Erythematosus.

Fig. 57. Case 525. Tendon sheath from palm. x 100. A strip of tendon (top) is covered by oedematous tissue in which there is deposition of fibrin and degeneration of collagen fibres. Only slight round cell response is seen.

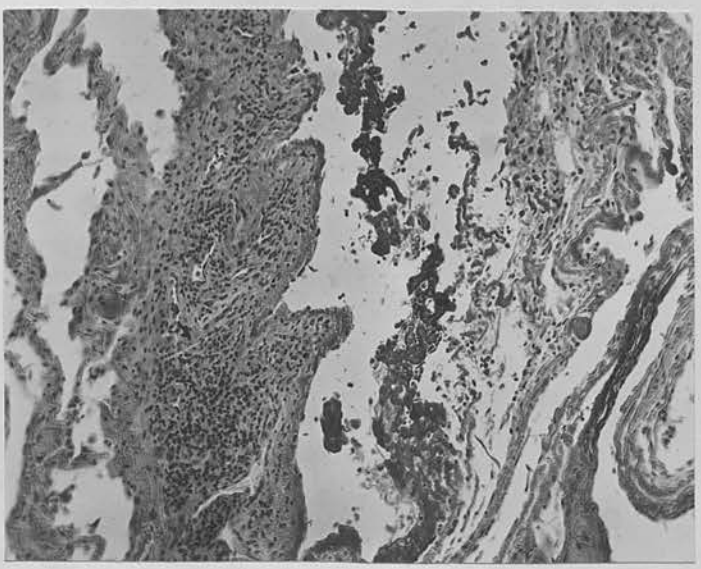

Fig. 58. Case 526. Tendon sheath from palm. x 100. Villous hyperplasia with extensive necrosis of surface and moderate lymphocytic infiltration (left). Fibrin deposition and swelling of collagen (right).

focus of proliferating mesenchymal cells of synovial type was seen deep to the surface (Case 526, Fig. 59).

Non-specific Tenosynovitis.

The lesions here showed the same wide range as in non-specific synovitis of joints. Mild subacute or chronic inflammation was seen in many cases, without any hyperplasia. However, all the features seen in the joints and tendon sheaths in rheumatoid arthritis were present in 13 cases, with necrosis in five of these (Table XIV and Figs. 60 & 61). A further 14 showed evidence of activity, but lacked one or more of the features of the complete picture. No evidence of generalised rheumatic disease could be elicited in these cases, most of which were traumatic in origin.

Tuberculous Tenosynovitis.

As in the joints, the diagnosis of tuberculosis was always quite definite, though tubercles were scanty in some cases. In two cases, parts of the specimen presented appearances identical with those seen in rheumatoid arthritis and non-specific tenosynovitis.

DISCUSSION.

This study has failed to reveal any lesion of synovial tissue which is specific to rheumatoid arthritis. The combination of lesions regarded by/

Synovial Tissue in Systemic Lupus Erythematosus.

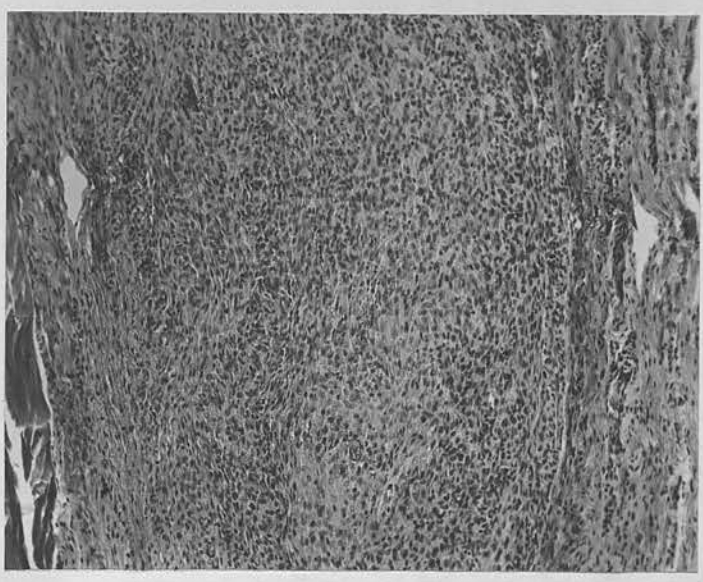

Fig. 59. Case 526. x 100. Another section from palmar tendon sheath. Focal proliferation of large mesenchymal cells close to tendon (bottom, left). Slight round cell infiltration is also seen.

where Lesions resemble those of Rheumatoid Arthritis.

Case No.	Site	Duration	Histological Features							
			a	b	c	d	e	f	g	other features
825	tibialis posterior	1 yr.	+	+	sm	+	+			
827	dorsum of wrist	6 yrs.	+	+	+	+	+		+	
		4 y. later	+	+	diff	+	+			
829	dorsum of wrist	?	+	+	+	+	+	+		
831	dorsum of wrist	5 yrs.	+	+		+	+		+	
832	wrist	6 mths.	+		+	+	+			
835	wrist	?			+	+	+	+		
839	right third finger	1 mth.			sm		+		+	
843	wrist (palmar)	1 yr.	+	+	+	+	+			
844	wrist	?	+	+	+	+	+		fine	
845	dorsum of wrist	?	+	+	+	+	+			
846	extensor pollicis	18 mths.	+		diff	+	+		+	
848	dorsum of wrist	mths.	+	+	diff	+	+		+	
850	palm of hand	?	+	+	diff	+	+			
857	dorsum of wrist	wks.	+	+	+	+	+	+		
858	dorsum of hand		+	+	+	+	+	+		also diffuse granulation tissue
860	dorsum of wrist	1 yr.	+	+	+	+	+	+		
863	wrist (palmar)	7 mths.	+	+	sm	+	+	+	+	
867	wrist	3 mths.	+	+	+	+	+	+		
868	both wrists	3 yrs.	+	+	+	+	+	+		
870	wrist	6 wks.	+	+	+	+	+	+		also diffuse granulation tissue
875	wrist	6 wks.	+	+	diff	+	+	+		
878	dorsum of wrist	3 wks.		+	+		+	+		
884	dorsum of wrist	7 yrs.	+		sm		+		fine	
890	wrist	1 mth.	+	+	diff	+	+	+		many polymorphs
892	dorsum of wrist	4 mths.	+	+	+	+	+			
893	dorsum of wrist	4 mths.	+	+	diff	+	+			
894	dorsum of wrist	1 yr.	+	+	+	+	+			

Key to Histological Features - See Table IV, p. 21.

Synovial Tissue in Non-specific Tenosynovitis.

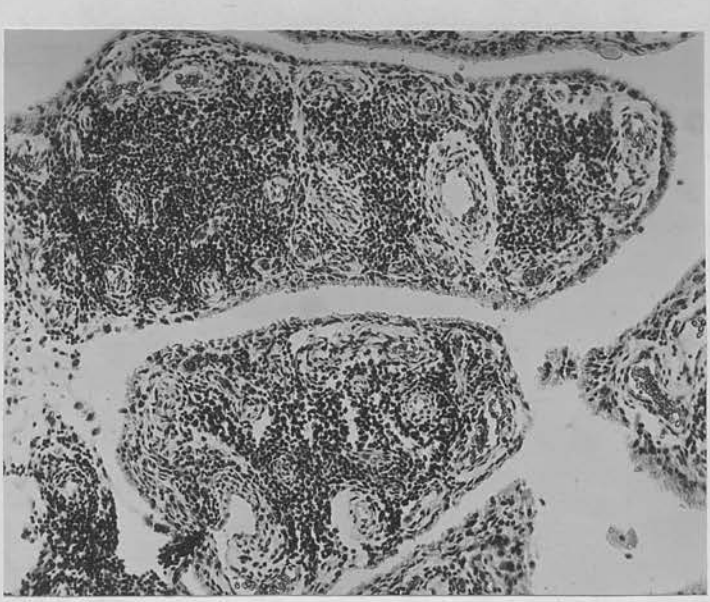

Fig. 60. Case 892. Tendon sheath from dorsum of wrist. x 100. Villous hyperplasia, congestion and massive round cell infiltration. Compare with Figs. 54-56.

Fig. 61. Case 863. Tendon sheath from palmar surface of wrist. x 50. The same features as in Fig. 60 are present but are distorted by marked oedema.

by Collins (1949 (b)) as diagnostic of the disease were found in only 24 out of 84 joints examined (29 per cent), and in three out of four biopsies from tendon sheaths. In only 50 per cent of the cases of clinically active rheumatoid arthritis (16 out of 33 cases - Table VIII) was the full combination of histological features seen. The same features were present in ankylosing spondylitis, pure osteoarthritis, recurrent synovitis, tears of menisci, non-specific bursitis and isolated non-specific tenosynovitis (Table XV). This table shows in addition, that the incidence of the "characteristic" changes of rheumatoid arthritis is not noticeably higher in that disease than in ankylosing spondylitis, non-specific synovitis or tears of menisci. Indeed, in only 24 out of 41 cases (59 per cent) where the "characteristic" lesions of rheumatoid arthritis were found in synovial tissue of joints was that disease present. As might be expected, appearances in which one or more of the "characteristic" changes was absent were seen in an even larger number of cases and a wider variety of diseases (Table XVI). The writer is therefore in agreement with Bennett (1952) who stated that the most that can be said of the lesions in synovial tissue is that they are consistent with rheumatoid arthritis.

An attempt was made to see whether the histological features could be correlated with the duration, stage and clinical activity of the

disease/

Incidence of Lesions " Characteristic " of Rheumatoid Arthritis in various Diseases of Synovial Tissue.

Diagnosis	Total number of specimens examined.	Histological Features of Rheumatoid Arthritis present	
		No.	Per cent.
1. Joints			
Rheumatoid arthritis	84	24	29
Ankylosing spondylitis	11	3	27
Osteoarthritis	31	1	3
Non-specific synovitis	41	9	22
Tears of Menisci	28	4	29
Total	195	41	21
Tuberculous arthritis	35	2*	
2. Bursae.			
Rheumatoid arthritis	8	0	0
Non-specific bursitis	114	3	3
3. Tendon Sheaths.			
Rheumatoid arthritis	4	3	75
Systemic lupus erythematosus	2	0	0
Non-specific tenosynovitis	75	13	17
Total	81	16	20
Tuberculous tenosynovitis	27	2*	

* "Characteristic" features present in places only : evidence of tuberculosis as well.

Table XVI.

Incidence of Lesions lacking One or More Features " Characteristic " of Rheumatoid Arthritis in various Diseases of Synovial Tissue.

Diagnosis	Total number of specimens examined.	Histological Features Suggestive of Rheumatoid Arthritis present	
		No.	Per cent.
1. Joints.			
Rheumatoid arthritis	84	30	36
Ankylosing spondylitis	11	3	27
Osteoarthritis	31	2	6
Gout	5	1	20
Systemic lupus erythematosus	8	1	12
Non-specific synovitis	41	2	49
Loose bodies in joint	7	2	29
Septic arthritis	7	2	29
Tears of menisci	28	3	11
Syphilitic arthritis	2	1	50
Total	224	47	20
2. Bursae.			
Rheumatoid arthritis	8	5	62
Non-specific bursitis	114	2	2
Total	122	7	6
3. Tendon sheaths.			
Rheumatoid arthritis	4	1	25
Systemic lupus erythematosus	2	1	50
Non-specific teno-synovitis	75	14	19
Total	81	16	20

disease in the affected joints. (Tables VI to VIII). This information was available in only some of the cases, so that statistical analysis was not possible. However, it is obvious that there is a tendency for histological evidence of activity to be present in a higher proportion of cases of short duration than in long-standing cases (Table VI). That the same tendency is seen in relation to the stage of the disease (Table VII) is to be expected for in most cases there is a direct relationship between the duration and the degree of damage in a joint (stage). A similar correlation was found between histological features and the clinical evidence of activity - pain, swelling, stiffness (Table VIII).

It should be noted that the inability to find a specific lesion was based on a study of material obtained mainly from established cases of rheumatoid arthritis. The joints had been affected for less than a year in only 8 of the 44 cases in which the duration was known (Table VI). Nevertheless, the course of the disease is such that clinical evidence of activity was present in over fifty per cent of the joints examined (Table VIII) and the histological features in well over a half of the joints were indicative of activity rather than the end results of the disease. None of the studies reviewed earlier in this section dealt with the initial phases of the disease, so that no information is available about the earliest

synovial/

synovial lesions. The recent introduction of an instrument whereby samples of synovial tissue can be obtained without open operation (Polley and Bickel, 1951) should enable this gap in our knowledge to be filled.

In addition to the non-specific subacute or chronic inflammation already discussed, a few cases of rheumatoid arthritis showed lesions in the synovial tissue with the same features as the subcutaneous nodule of that disease. Such appearances have been described previously in isolated cases by Bennett et al (1940) and Kersley and Gibson (1952). The specificity of the subcutaneous nodule will be discussed in detail in Section III of this thesis, so that it will be sufficient to say here that its histological structure is not completely specific. The occurrence of such a lesion in the synovial tissue in the presence of clinical features suggestive of rheumatoid arthritis is probably diagnostic of that disease, to the exclusion of other rheumatic diseases such as ankylosing spondylitis, rheumatic fever, systemic lupus erythematosus and polyarteritis nodosa.

The appearances found here in synovial tissue in juvenile rheumatoid arthritis and " Felty's syndrome"support the opinion that these diseases are merely variants of rheumatoid arthritis. Although the appearances in one of the two cases of juvenile rheumatoid arthritis (Case 43, Fig.16) were/

were not particularly suggestive of adult rheumatoid arthritis, they did not indicate any more specific aetiology and similar lesions were seen in the adult form of the disease. The occurrence of numerous polymorphs (Fig. 9) and evidence of old or recent haemorrhage in several cases of otherwise typical rheumatoid arthritis in which there was no evidence of psoriasis fails to support the opinion of Hench (1948) that specific lesions occur in psoriatic arthritis.

All of the lesions of active rheumatoid arthritis were seen in ankylosing spondylitis. Furthermore these two diseases show essentially similar features in other joint tissues (Cruickshank, 1951). These findings could be held to support the current opinion mentioned previously, that spondylitis is merely a variant of rheumatoid arthritis. This opinion is based almost entirely upon resemblances in the clinical and histological features in peripheral joints. It does not take into account differences in the type of individual affected, in the sex incidence, in the anatomical distribution in typical cases, and in the reaction to different forms of treatment - differences which are much greater than those seen in juvenile rheumatoid arthritis and "Felty's Syndrome." Even allowing that the histological changes are similar, there are numerous examples of diseases, whose aetiology is known to be different, in which the tissue reactions follow a common pattern. As

the aetiology of both rheumatoid arthritis and ankylosing spondylitis is unknown, it is preferable to regard them as separate entities.

The occurrence of urate deposits with the characteristic tissue reaction was seen only in gout. This follows the general opinion that this lesion is diagnostic. Nevertheless, the appearances in parts of the synovial tissue in one case showed a distinct resemblance to rheumatoid arthritis as was noted by Collins (1938(a)) and Sherman (1946). The same tendency was seen in tuberculosis, where characteristic lesions were always seen, though parts of the tissue had an appearance identical with rheumatoid arthritis.

Most of the lesions seen in rheumatic fever were completely non-specific. The patches of necrosis, such as were seen in some cases, cannot be regarded as a specific lesion, for very similar changes were seen in systemic lupus erythematosus. Necrosis was also a feature in some cases, of rheumatoid arthritis, ankylosing spondylitis, non-specific synovitis, tears of menisci, non-specific bursitis and post-traumatic tenosynovitis, where it was sometimes much more extensive than in rheumatic fever. In one case of rheumatic fever, focal necrosis of the synovial tissue had excited a localised infiltration with lymphocytes and histiocytes (Fig. 31). This lesion bore little resemblance to the subcutaneous nodule of rheumatic fever (See Section III) or to the myocardial Aschoff/

Aschoff body, so can hardly be regarded as specific.

The pathological changes seen in joints in systemic lupus erythematosus were more severe than those of rheumatic fever, although one of the cases was diagnosed clinically as such for some time (Case 523, Fig. 37). In another, where the clinical features were more suggestive of rheumatoid arthritis than rheumatic fever, the lesions bore a very close resemblance to those of the former disease (Case 526, Fig. 35). Histological examination of synovial tissue is thus of no value in establishing a diagnosis of lupus. The discovery of the "LE cells" in the bone marrow (Hargraves et al, 1948) and the ease with which they can be produced by mixing normal blood cells with serum from cases of the disease (Hargraves, 1949) has provided a more ready means of diagnosis, for this phenomenon appears to be almost specific to the disease (Lee et al, 1951). The occurrence of lesions in the tendon sheaths in this disease has not been described previously and was quite unsuspected clinically. They differed from the lesions in this situation in rheumatoid arthritis in the large amount of fibrin present and relatively less intense inflammation. However, the changes were not specific, and they were not of much diagnostic value.

The paucity of lesions in synovial tissue in polyarteritis nodosa, makes examination of such material/

* A clinical picture closely resembling rheumatoid arthritis has also been described in lipoidosis of the joints and subcutaneous tissue (Graham and Stansfield, 1946).

material of little diagnostic value. The chance finding of the typical vascular lesions, in the acute phase - not encountered in this study - would, of course, be diagnostic for similar lesions have not been recorded in this tissue in other diseases.

Histological examination of synovial tissue in patients presenting with clinical features of rheumatic disease is occasionally useful in eliminating such disease. This was seen in Case 925 of the present series where the diagnosis of amyloidosis of the knee and muscles was made. There are 13 cases on record in which such amyloid deposits occurred in association with multiple myeloma (Stewart, 1938 ; Tarr and Ferris, 1939). Nearly all these patients were diagnosed clinically at one time or another as rheumatoid arthritis. In some the confusion was increased by the presence of subcutaneous deposits of amyloid on the forearms in the situation where subcutaneous nodules most frequently occur in rheumatoid arthritis. The true diagnosis was not suspected in the present case until the histological preparations were studied. The small piece of bone marrow examined showed no evidence of myeloma. Unfortunately the patient was not Xrayed during the two days that she was in hospital before death.

The high incidence in non-specific teno-synovitis of lesions identical with or closely resembling those of rheumatoid arthritis (27 out of 75 cases) might be held to support the view that this/

this condition be grouped among the rheumatic diseases (von Albertini, 1929 ; Klinge, 1933(a)). This view appears to have been based entirely on the histological resemblance between the conditions. Most of these patients were traced and enquiry from the family doctor failed to reveal evidence of anything more than the local complaint. It does not seem likely, therefore, that these examples of isolated tenosynovitis represented a localised manifestation of a general rheumatic disease particularly when it is considered that most of them were caused by trauma. Nevertheless, this study provided support for Baumgartner's (1946) observation that rheumatoid arthritis may commence as tenosynovitis. This was the initial feature in Case 63, (Fig.55), where it preceded joint involvement by several months and was regarded clinically as tuberculous when biopsy was performed 11 months after the onset.

It is obvious from the foregoing results and discussion that histological examination of synovial tissue is of limited value in diagnosis of rheumatic diseases. A definite diagnosis can be made only in gout and in polyarteritis nodosa if the vascular lesions are encountered. Confirmation of the diagnosis of rheumatoid arthritis is occasionally possible if lesions of the subcutaneous nodule type are encountered; in most cases the findings are only consistent with a diagnosis made on other grounds. No help can be given/

given in differentiating systemic lupus erythematosus from rheumatoid arthritis or rheumatic fever.

SUMMARY.

1. The literature on lesions of the synovial tissue of joints, bursae and tendon sheaths in rheumatic diseases has been reviewed. There is considerable difference of opinion as to whether lesions occur which are specific to rheumatoid arthritis and its variants, such as juvenile rheumatoid arthritis ("Still's disease") and "Felty's syndrome." There are a few references to the histology of ankylosing spondylitis, several of which have given rise to a rather widely held opinion that this disease is only a variant of rheumatoid arthritis. The lesions of osteoarthritis, gout, and rheumatic fever are fairly well defined. Little is known about changes in this tissue in systemic lupus erythematosus or polyarteritis nodosa.

2. The object of this study was to determine the value of histological examination of synovial tissue in the diagnosis of rheumatic diseases.

3. The material studied included synovial tissue from 84 joints, 8 bursae and 4 tendon sheaths from 66 cases of rheumatoid arthritis, 11 joints from 8 cases of ankylosing spondylitis, 31 joints from 27 cases of pure osteoarthritis, 5 joints from/

from 2 cases of gout, 13 joints from 11 cases of rheumatic fever, 8 joints and 2 tendon sheaths from 4 cases of systemic lupus erythematosus, and 5 joints from 3 cases of polyarteritis nodosa. This was compared with material from a single joint in 146 cases of non-rheumatic disease, consisting of 41 cases of non-specific synovitis, 7 of loose bodies in joints, 7 of septic arthritis, 4 of osteochondritis, 28 tears of menisci, 19 cysts of menisci, 2 cases of haemophilia, 2 cases of syphilitic arthritis and 1 case of amyloidosis of joint and muscle and with material from 114 cases of non-specific bursitis, 6 cases of tuberculous bursitis, 75 cases of non-specific tenosynovitis and 27 cases of tuberculous tenosynovitis.

4. The only specific lesion encountered was the urate deposit of gout.

5. Lesions which had been described previously as specific to rheumatoid arthritis were found in ankylosing spondylitis, pure osteoarthritis, recurrent synovitis, tears of menisci, non-specific bursitis and non-specific tenosynovitis. The incidence of lesions "characteristic" of rheumatoid arthritis was not significantly higher in this disease than in several of the others mentioned. In cases of rheumatoid arthritis histological evidence of activity was correlated with duration, stage and clinical activity in affected joints. Lesions in synovial tissue in/

in juvenile rheumatoid arthritis and "Felty's Syndrome" were the same as in typical adult rheumatoid arthritis.

6. In ankylosing spondylitis the lesions were the same as in rheumatoid arthritis. Reasons are given for regarding the two diseases as separate entities.

7. No lesions were found which were specific to rheumatic fever or lupus erythematosus. Histological examination of synovial tissue is of no value in establishing the latter diagnosis. Lesions of tendon sheaths in lupus are described for the first time.

8. Lesions were scanty in polyarteritis nodosa, only the healed stage being seen.

9. A case of amyloidosis of the left knee and skeletal muscles is recorded, in which the clinical features were indistinguishable from rheumatoid arthritis. Previous reports are quoted in which amyloidosis of this distribution was associated with multiple myeloma.

10. Although there is a high incidence in non-specific tenosynovitis of lesions similar to those of rheumatoid arthritis, reasons are given for regarding these cases of non-rheumatic aetiology.

11. The limitations of histological examination of synovial tissue in diagnosis of rheumatic diseases are defined.

SECTION II.

The Need for Caution in the Interpretation of Multiple Biopsies of Synovial Tissue in Rheumatic Diseases.

INTRODUCTION.

The introduction of cortisone and ACTH to clinical medicine (Hench et al, 1949) has raised the question whether the dramatic improvement induced by them is associated with changes in the tissues. Several reports have appeared in which it is claimed that synovial tissue taken from joints during, or after, administration of the hormones showed changes attributable to their action (Hench et alii, 1949 and 1950 ; Giansiracusa et alii, 1951 ; Polley and Bickel, 1951). Giansiracusa et alii were cautious about the interpretation of the histological appearances, whereas Hench et alii (1950) accepted decrease in the amount of inflammation, oedema, necrosis or surface hyperplasia as due to the hormones. Polley and Bickel also described histological evidence of improvement in specimens obtained by means of an instrument for punch biopsy of joints.

No mention was made in the reports quoted about natural variations in the histological appearances in synovial tissue in rheumatic diseases. Previous workers had mentioned the fact that/

that synovial tissue taken simultaneously from different parts of the same joint in rheumatoid arthritis showed varying appearances (Allison and Ghormley, 1931(b); Parker and Keefer, 1935 ; Ghormley, 1938 ; Jordan, 1938; Rosenberg, 1949). These writers laid little stress on these naturally occurring variations which reflect the chronic character of the disease with alternating phases of activity and remission. Indeed this point was of little practical importance until the question of the effect of hormones on the histology was raised. The likelihood that future studies of synovial tissue may be made upon specimens obtained blindly by the punch biopsy instrument rather than by open operation makes it even more necessary to appreciate the naturally occurring variations.

The purpose of this part of the thesis is to demonstrate the variations in the histopathology of synovial tissue taken at the same time from different parts of joints in rheumatoid arthritis, ankylosing spondylitis, gout, rheumatic fever, systemic lupus erythematosus and polyarteritis nodosa. Particular attention has been paid to features which might be interpreted as an effect of treatment with drugs.

MATERIAL AND METHOD.

The material studied was taken from the same cases as in Section I and represents those cases in which multiple blocks were available. The tissue was/

was obtained at open operation or post mortem. The anatomical distribution of the material is shown in Table XVII . In the knee, blocks were taken from the suprapatellar pouch, medial or lateral compartment or infrapatellar pad in every case. Additional blocks were taken from one or other meniscus in several cases. In nine cases of rheumatoid arthritis, two adjacent blocks were taken from one or other of the regions mentioned. An average of three blocks was taken from different regions of the other joints.

In assessing variations in the histological appearances due consideration was given to the variations in normal histology, of synovial tissue from different regions of the joints (Key, 1932). Comparisons of the appearances in different sections in rheumatoid arthritis and ankylosing spondylitis were made by using the same criteria as in Section I. In the other diseases, the occurrence and degree of proliferation, inflammation necrosis and fibrosis were noted.

RESULTS.

Rheumatoid Arthritis. (Table XVIII).

In sixteen of the joints, the various sections showed the same features, or differed only in minor points, such as the degree and extent of surface hyperplasia or the degrees of oedema and congestion. Nine joints showed more noticeable variations, such/

Table XVII.

Anatomical Distribution of Synovial Tissue in Cases of Rheumatic Disease where Multiple Blocks were obtained from Joints.

Diagnosis	Total Joints	Joint					
		Shoulder	Elbow	Prox. inter-phalangeal	Hip	Knee	Sterno-clavicular
Rheumatoid arthritis	35	3	3	1		28	
Ankylosing spondylitis	6				4	1	1
Gout	1					1	
Rheumatic fever	10		1			9	
Systemic lupus erythematosus	4					4	
Polyarteritis nodosa	4					4	
Total	60	3	4	1	4	47	1

Histological Features in Multiple Blocks of Synovial Tissue from Joints in Rheumatoid Arthritis.

Case No.	Total Duration	Interval between last therapy and time of taking tissue	Affected Joint: Duration	Stage	Clinical Activity	Source of Tissue		Histological Features: a	b	c	d	e	f	g	Normal
1	9 yrs.	8 yrs.	?	III	Active	Shoulder				+		+	+	fine	
										+		+	+	fine	
			?	IV	Inactive	Knee *	S					+		+	
							L			sm		+		+	
							F				+	+		+	
4	10-12 y.	1 yr.	?	?	Inactive	Shoulder						+			+
												+			+
									+			+		+	
			?	II	Active	Knee	S				+	+		+	
							L	+	+	sm	+	+	+		
							M		+	sm	+	+			
							F	+	+	+	+	+		fine	
							C	+	+	+	+	+		fine	
5	20 yrs.	Not known	?	?	Inactive	Knee	S			sm		+	+		
							L			sm		+			
							F	+	+	sm	+	+			
6	18 yrs.	12 yrs.	? 1 yr.	III	Active	Knee	S	+	+	+	+	+			
							L	mainly granulation tissue : partly as above							
							F	+	+	+	+	+			
7	2 yrs.	Not given	< 2 yrs	II	Active	Shoulder		+	+	+	+	+		fine	
										sm		+	+	+	
			2 yrs.	II	Active	Knee	S	+		+	+	+		fine	
							L			sm		+			
							F	+		+	+	+		fine	
8	8 yrs.	Not known	?	II	Inactive	Knee	S			sm		+		+	
							M					+	+	+	
							F	+	+		+	+	+		
9	>8 yrs.	Not known	?	II	Active	Elbow		+		+	+	+	+		
												+	+	+	
								+		sm	+	+	+		
10	?	2 yrs.	?	?	?	Knee	S								+
							L								+
							F								+
12	32 yrs.	Not known	30 yrs	?	?	Knee	S	+			+	+	+	fine	
							L			sm		+		+	
							M			sm		+			
							F	+		sm		+		fine	
13	5 yrs.	Not given	5 yrs		Active	Knee	S			sm	+	+	+		
							L			sm	+	+			
							F			+		+	+		
							F			+		+	+	+	
15	13 yrs.	Not given	13 yrs	III	Active	Elbow		+	+	+	+	+	+		
								+	+	+	+	+	+		

16	?	Not known	?	?	?	Knee	S					+	+	sl	
							M					+	+	sl	
							F					+	+	sl	
18	2½ yrs	Not given	2½ yrs	I	Active	Prox. interphalangeal		+	+			+		fine	
									+	+	+	+			
			2 yrs	II	Inactive	Knee	S	+	+		+	+			
							L	+	+	+	+	+	+		
							F	+	+	+	+	+	+		
19	10 yrs	3 yrs	<10 yrs	II	Active	Knee	S		+	sm	+	+			
							M	+	+	+	+	+	+		
							F	+	+	sm	+	+		fine	
20	1 yr	Not given	< 1 yr.	I-II	Active	Knee	S	+		diff	+	+	+	+	
							L	+		sm	+	+	+	+	
							L			sm		+		+	
							F	+		diff	+	+	+		
23	8 yrs	Not given	1 yr	II	Active	R. Knee	S		+	sm	+	+	+	+	
							S					+	+		
			< 1 yr.	II	Active	L. Knee	S	+	+	+	+	+			
							S	+		+	+	+	+	fine	
24	4 yrs.	Not known	< 4 yrs	?	Inactive	Knee	S					+		+	
							M	+	+			+		fine	
							F					+		+	
							C	+				+		fine	
25	1½ yrs.	Not given	?	II	Active	Knee	S	+	+		+	+	+		
							M		+		+	+			
							F		+		+	+			
26	?	Not given	?	II	Inactive	Knee	S					+			+
							L					+			+
							F					+		+	
27	many years	Not given	?	?	Inactive	Knee	S	+				+		+	
							L					+		+	
							M	+	+			+			
							F					+		+	
37	3 yrs	Not given	3 yrs	?	?	Knee	S	+		+	+	+	+		
							L	+		+	+	+			
							F	+		+	+	+	+		
39	3 yrs	Not given	3 yrs	?	Active	Elbow		sl	+	+	+	+			
								+	+	+	+	+	+		
								+	+	+	+	+	+		
40	many	1 wk.	?	II	Active	Knee	S	+	+	sm	+	+	+	fine	
							L	+	+	sm	+	+	+	fine	
							L	+		sm	+	+		+	
							F	+						+	
41	5 yrs	Not given	? 5 yr	IV	Inactive	Knee	S					+		+	
							M					+		+	
							F					+		+	
43	1 yr.	1 wk. (insulin)	1 yr	I	Active	Knee	S		+	sm	+	+		+	
							S	+	+	+	+	+			
							L			sm		+		+	
							F					+		+	
44	33 yrs	Not given	?	?	?	Knee	S								+
							M								+
							F								+

47	5 yrs	$4\frac{1}{2}$ yrs.	8 mth.	II	Inactive	Knee	S	+			+	+		+	
							L	+			+	+		+	
							F	+			+	+		+	
49	7 yrs	4 yrs	2 yrs	II	Active	Knee	L		+	sm	+	+		+	
							L	+	+	+	+	+			
							M			sm		+		+	
							M					+		+	
50	7 yrs	Not given	3 yrs	II	Active	Knee	S		+	+	+	+			
							S		+	+	+	+	+	+	
54	11 yrs	Not given	?	?	Active	Knee	S	+	+	+	+	+			
							S					+		+	

Key :

o = gold used unless stated

* = the letters in this column refer to the region from which tissue was taken, i.e.,

S = suprapatellar

L = lateral compartment

M = medial compartment

C = meniscus

Histological Features - as in Table IV, p. 21.

such as the presence of necrosis in only one section, the presence of diffuse granulation tissue alternating with more typical appearances (Case 6, Figs. 62 and 63), or variations in the number and distribution of lymphocytes and plasma cells.

Major variations in the histological appearances were seen in ten of the joints. Thus in a knee (Case 54), one section showed marked hyperplasia and intense inflammation (Fig. 64), whereas a section from an adjacent part of the synovial tissue showed well marked fibrosis (Fig. 65). In another knee (Case 21), fibrosis was predominant in one section, slight in another and absent from a third. Three sections from an elbow (Case 39) showed, respectively, marked inflammation without fibrosis, slight inflammation without fibrosis and marked fibrosis without inflammation. Variations in the relative degrees of inflammation and fibrosis, which might be interpreted as indicative of activity and healing respectively, were seen in eight joints. Such variations were seen not only in blocks from different regions of a joint (Case 7, Figs. 66 and 67), but sometimes in adjacent blocks from the same region (See Figs. 64 and 65) and occasionally in a single section. They were found in juvenile rheumatoid arthritis (Case 43, Figs. 68 and 69) as well as in the adult.

The cases were analysed as in Section I to see whether the variations in the histological appearances/

Synovial Tissue in Rheumatoid Arthritis.

Fig. 62. Case 6. Knee (lateral compartment). x 40. Villous hyperplasia, thickening of surface layer, congestion, massive round cell infiltration and necrosis (the dark areas, left and right).

Fig. 63. Case 6. Another field from same section as Fig. 62. x 100. No villi or synovial surface, but much diffuse granulation tissue.

Synovial Tissue in Rheumatoid Arthritis.

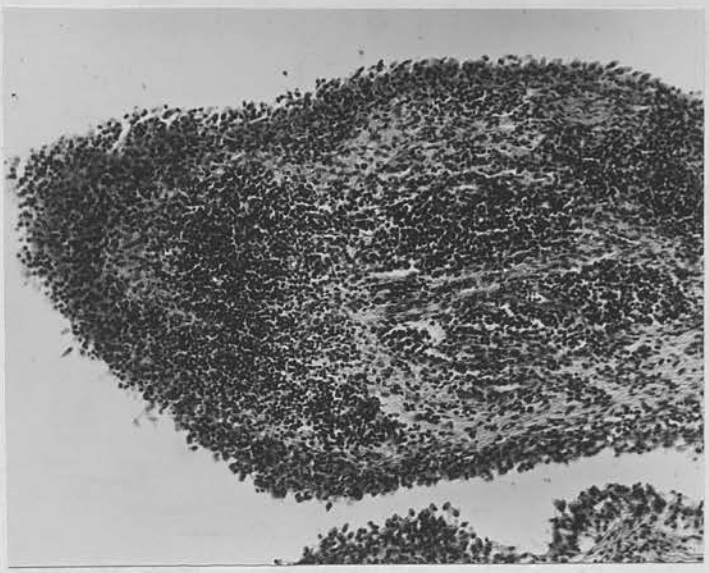

Fig. 64. Case 54. Knee (suprapatellar). x 100. One of many villi showing hyperplasia of surface cells, oedema, congestion and massive infiltration with round cells.

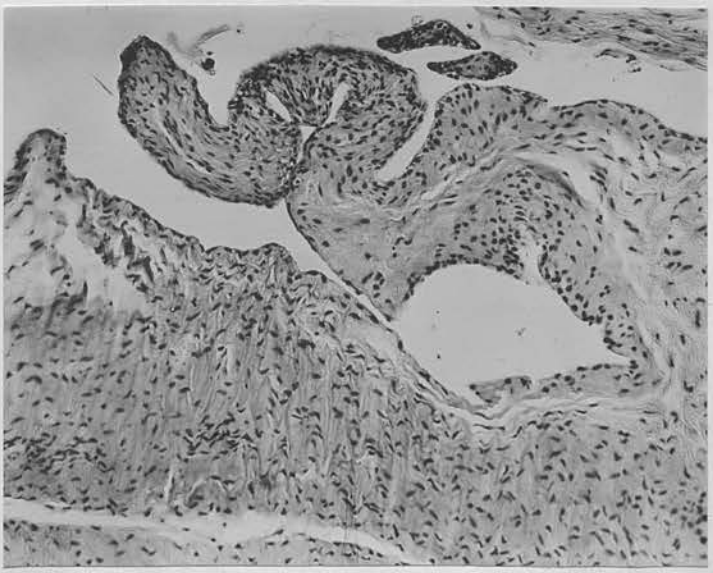

Fig. 65. Case 54. Section from adjacent block to Fig. 64. x 100. Cellular fibrosis with minimal lymphocytic infiltration in places.

Synovial Tissue in Rheumatoid Arthritis.

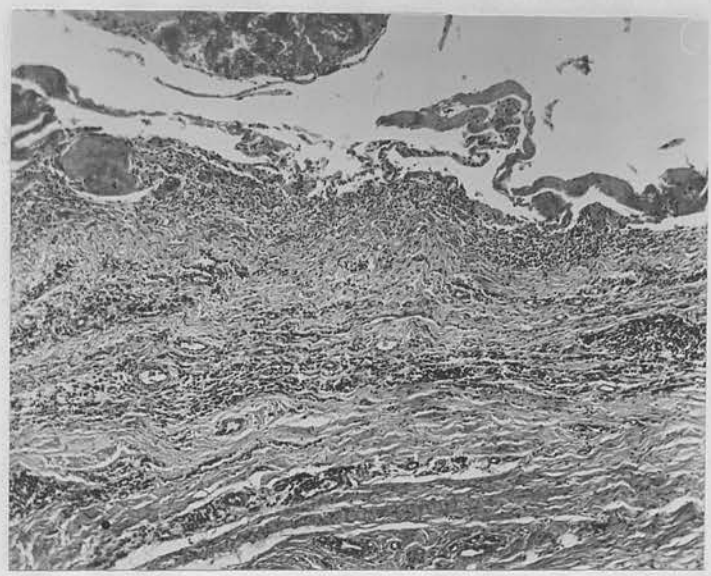

Fig. 66. Case 7. Knee (suprapatellar). x 50. Necrosis of superficial tissue (top), diffuse round cell infiltration, congestion and some fibrosis of deeper tissue.

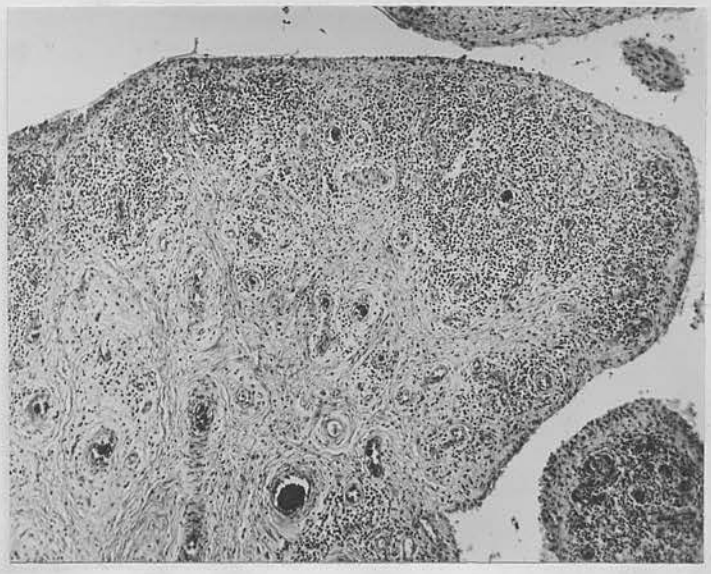

Fig. 67. Case 7. Knee (lateral compartment) x 50. Large villus, showing fine fibrosis superimposed upon congestion and diffuse round cell infiltration.

Synovial Tissue in Juvenile Rheumatoid Arthritis.

Fig. 68. Case 43. Knee (suprapatellar). x 120. Congestion, oedema, diffuse subacute inflammation and some degeneration of surface layer. Minimal fibroblastic proliferation.

Fig. 69. Case 43. Section from adjacent block to Fig. 68. x 100. Marked fibrosis with only slight inflammation.

appearances could be correlated with the duration, stage and activity of the disease in the affected joints (Tables XIX to XXI), or with drug therapy (Table XXII).

Ankylosing Spondylitis (Table XXTII).

The variations in appearance seen here were of minor degree only. This may be due to the fact that a substantial degree of inflammation was seen in only two joints.

Gout.

Two sections from the knee of a case of gout (Case 243) showed striking differences, inflammation being predominant in one (Fig. 70) and fibrosis in the other (Fig. 71).

Rheumatic Fever.

The appearances in two of these joints were normal. In another four, the lesions were mild, consisting of congestion, slight hyperplasia of the synovial cells, minimal round cell infiltration and occasional patches of necrosis of the surface. More marked changes, including patches of necrosis in the deeper tissues or slight villous hyperplasia, both with round cells and histiocytes response were seen in four joints. Two knees showed appearances in different sections varying from patchy necrosis in one section, congestion and slight round cell infiltration in a second to fibrosis in a third (Figs. 72-74). In only one of these cases had there been a previous attack of rheumatic fever.

Systemic/

Table XIX.

Relationship of Duration of Rheumatoid Arthritis in Joints to Variations in Histology in Synovial Tissue from Different Regions of Joints.

Degree of Variation in Histology	Total	Duration							
		< 1 yr		1-2 yrs.		2-5 yrs.		> 5 yrs	
		No.	%	No.	%	No.	%	No.	%
Minor	7	1	14	0	0	5	71	1	14
Moderate	7	1	14	3	43	2	29	1	14
Major	7	1	14	4	57	1	14	1	14
Total	21	3	14	7	33	8	38	3	14

Table XX.

Relationship of Stage of Rheumatoid Arthritis in Joints to Variations in Histology in Synovial Tissue from Different Regions of Joints.

Degree of Variation in Histology	Total	Stage							
		I		II		III		IV	
		No.	%	No.	%	No.	%	No.	%
Minor	7	0	0	2	29	3	43	2	29
Moderate	8	1	12	5	62	1	12	1	12
Major	8	2	25	6	75	0	0	0	0
Total	23	3	13	13	56	4	17	3	13

Table XXI.

Relationship of Clinical Activity of Rheumatoid Arthritis in Joints to Variations in Histology in Synovial Tissue from Different Regions of Joints.

Degree of Variation in Histology	Total	Cases Clinically Active	
		No.	%
Minor	12	5	42
Moderate	9	7	78
Major	9	8	89
Total	30	20	67

Table XXII.

Relationship between Administration of Gold and other Drugs in Rheumatoid Arthritis and Variations in Histology in Synovial Tissue from Different Regions of Joints.

Degree of Variation in Histology	Total	No gold given	
		No.	%
Minor	14	9	64
Moderate	9	4	44
Major	8	2	25
Total	31	15	48

Table XXIII.

Histological Features in Multiple Blocks of Synovial Tissue from Joints in Ankylosing Spondylitis.

Case	Total Duration	Affected Joint: Duration	Affected Joint: Stage	Affected Joint: Clinical Activity	Source of Tissue		Histological Appearances: a	b	c	d	e	f	g	Normal
6	?	?	? II	?	Hip						+	+		
											+	+		
											+	+		
7	12 yrs.	? 12 yrs.	III-IV	Active	R. hip		+	+	sm		+			
							+	+	+	+	+			
							+		sm	+	+			
					L. hip		+	+	+	+	+	+		
							+	+	+	+	+	+	fine	
									sm		+	+		
9	7 yrs.	< 7 yrs.	II	Inactive	Knee	S			sm			+	+	
						L			sm				+	
						M			diff				+	
						F							+	
						C	+			+	+			
	4 yrs.	5 mths.	II	Active	Sterno-clavicular						+		+	
							+				+		+	
							+	+			+	+	+	
	?	?	?	?	Hip		+	+	sm	+	+		+	
							+	+		+	+		+	
							+	+		+	+	+	+	
										+	+			

Key - See Table XVIII, p. 87.

Table XXIII.

Histological Features in Multiple Blocks of Synovial Tissue from Joints in Ankylosing Spondylitis.

ase o.	Total Duration	Affected Joint			Source of Tissue		Histological Appearances							
		Duration	Stage	Clinical Activity			a	b	c	d	e	f	g	Normal
96	?	?	? II	?	Hip						+	+		
											+	+		
											+	+		
97	12 yrs.	? 12 yrs.	III-IV	Active	R. hip		+	+	sm		+			
							+	+	+	+	+			
							+		sm	+	+			
					L. hip		+	+	+	+	+	+		
							+	+	+	+	+	+	fine	
									sm		+	+		
99	7 yrs.	< 7 yrs.	II	Inactive	Knee	S			sm			+	+	
						L			sm				+	
						M			diff				+	
						F							+	
						C	+			+	+			
01	4 yrs.	5 mths.	II	Active	Sterno-clavicular						+		+	
							+				+		+	
							+	+			+	+	+	
03	?	?	?	?	Hip		+	+	sm	+	+		+	
							+	+		+	+		+	
							+	+		+	+	+	+	
										+	+			

Key - See Table XVIII, p. 87.

Synovial Tissue in Gout.

Fig. 70. Case 243. Knee (lateral compartment) x 100. Round cell infiltration, necrosis (top right), metaplasia of cartilage (bottom left) and small urate deposits (bottom right).

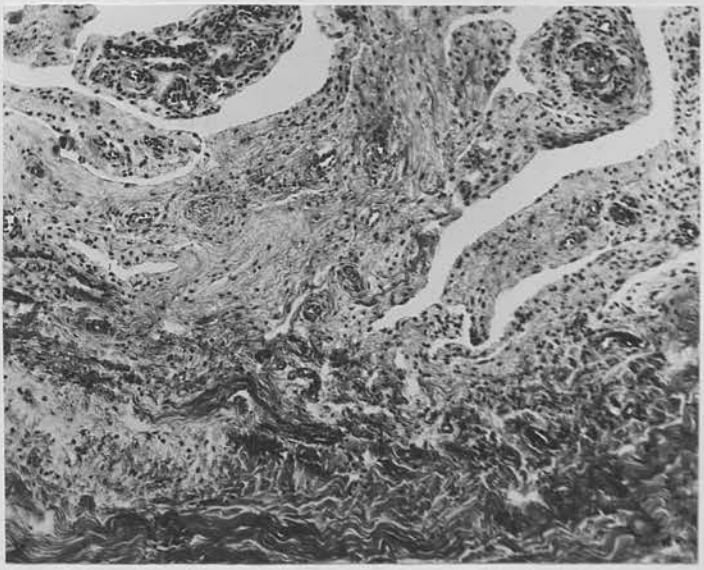

Fig. 71. Case 243. Knee (medial compartment). x 75. Villous hyperplasia and marked fibrosis.

Synovial Tissue in Rheumatic Fever.

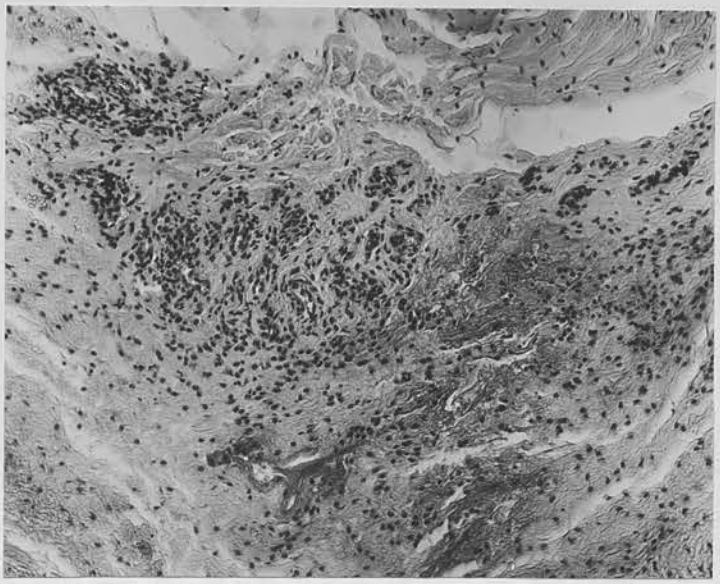

Fig. 72. Case 246. Elbow. x 100. Large area of necrosis (right) with round-cell response and congestion.

Fig. 73. Case 246. Another block from adjacent region to that shown in Fig. 72. x 100. Slight proliferation of surface cells, congestion, oedema and minimal lymphocytic infiltration.

Synovial Tissue in Rheumatic Fever.

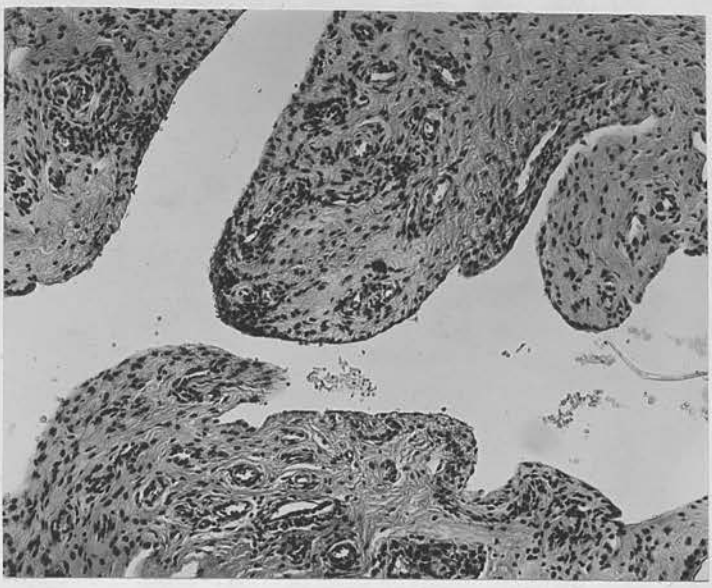

Fig. 74. Case 246. x 100. Section from a third block, showing villous hyperplasia and fibrosis with congestion, and slight lymphocytic infiltration.

Systemic Lupus Erythematosus.

The appearances in the different regions of two of the joints were the same and in a third minor variations were seen. In the fourth joint (Case 523) marked variations were seen, one region showing patchy surface necrosis with oedema and slight round cell infiltration (Fig. 75). In a block closely adjacent to this there was acute necrotising arteritis with marked acute inflammation (Fig. 76), whereas in another block fibrosis was the main feature (Fig. 77). These variations in histology were not related to therapy.

Polyarteritis Nodosa.

In two of the joints, the synovial tissue was healthy. In the other two, both from Case 542, occasional arteries and veins showed healed lesions. Slight fibrosis and thrombosis of many capillaries were also seen, but there was no evidence of acute lesions.

DISCUSSION.

This study shows that marked variations in the histological appearances in synovial tissue taken simultaneously from different regions or adjacent parts of a joint were not uncommon in rheumatoid arthritis. Minor variations, affecting particularly the relative amounts of inflammation and fibrosis, were frequently seen in the disease. Major/

Synovial Tissue in Systemic Lupus Erythematosus.

Fig. 75. Case 523. Knee (lateral compartment) x 100. Oedema and necrosis of superficial zone with lymphocytic reaction and congestion in deeper tissue.

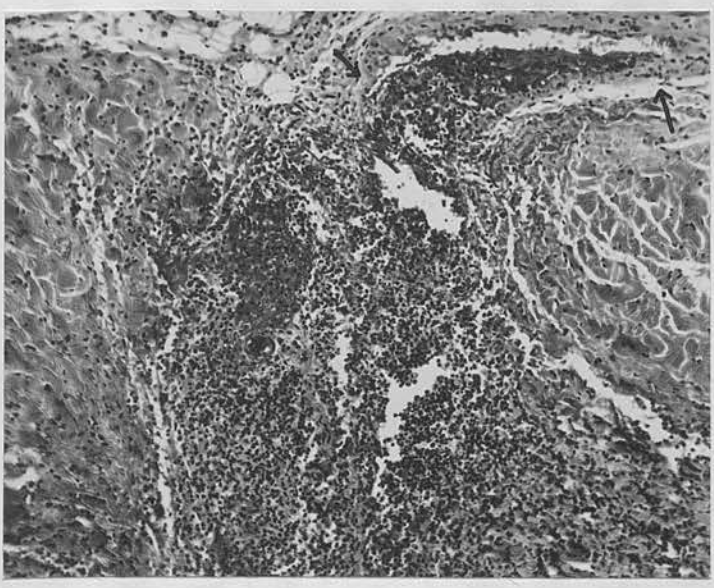

Fig. 76. Case 523. Another block from some region as Fig. 75. x 100. Normal wall of artery (top right) becomes necrotic at arrows and the lumen is thrombosed. Intense acute inflammation of adjacent tissue.

Synovial Tissue in Systemic Lupus Erythematosus.

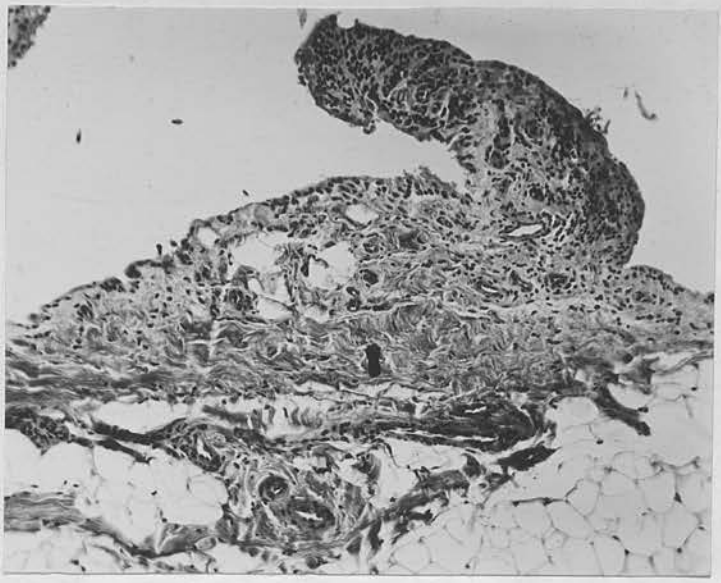

Fig. 77. Case 523. Knee (fat pad). x 100. Fibrosis and slight lymphocytic infiltration of a small villus.

Major variations occurred more often than minor ones in cases which were of short duration, clinically active or at an early stage of the disease, whereas minor variations were more frequent in cases of longer duration clinically inactive and at a later stage (Tables XIX to XXI). The degree of variation in the histopathology was not related to the administration of gold, for in over a third of those cases where moderate or marked differences occurred, no gold had been given.

Although only slight variations have been noted here in the appearances of sections from joints in ankylosing spondylitis, the close parallel between the lesions and the clinical course in that condition and in rheumatoid arthritis (Cruickshank, 1951) suggests that similar variations in histology might be expected to occur in spondylitis.

The lesions which occur in the synovial tissue in most cases of rheumatic fever and systemic lupus erythematosus are such that striking differences in the appearances in different parts of a joint are much less likely to occur than in rheumatoid arthritis. Indeed, Klinge (1931(a)) stressed that extensive search of many blocks of synovial tissue may be necessary in order to make a definite diagnosis of rheumatic fever. Nevertheless, this study has shown that, in both diseases, parts of the synovial tissue showed fine fibrosis, whereas

recent/

recent necrosis and inflammation were seen in others. In neither disease could the appearances be correlated with drug therapy. The synovial lesions in polyarteritis nodosa showed the same patchy distribution which is found elsewhere in the body in this disease. Furthermore, it is to be expected that vessels in the synovial tissue, just as those in other tissues, may show all stages of the disease from acute necrotising arteritis to completely healed lesions, even in cases which have had no treatment.

All the changes in the synovial tissue which have been reported in cases of rheumatoid arthritis receiving cortisone or ACTH, have been seen in this investigation to occur naturally in the course of the disease. Although the administration of these drugs may produce a dramatic clinical response, much caution must be exercised in attributing to them, or to other drugs which may be introduced in the future, changes which may, in fact, occur in the natural course of the disease. The same caution is necessary in other diseases which respond to the same drugs, such as systemic lupus erythematosus, rheumatic fever, gout and ankylosing spondylitis.

SUMMARY.

1. The introduction of potent therapeutic agents such as cortisone and ACTH has led to studies of of the histology of synovial tissue in rheumatoid arthritis before and during or after therapy.

Claims/

Claims have been made that differences between the appearances in this tissue are due to the action of the hormones.

These claims have not taken into account variations which may occur naturally in the disease.

2. Multiple blocks have been taken at one time from different regions of 60 joints, 35 being affected by rheumatoid arthritis, 6 by ankylosing spondylitis, 1 by gout, 10 by rheumatic fever, 4 by systemic lupus erythematosus and 4 by polyarteritis nodosa.

3. Major variations were seen in the appearances in different regions of 10 joints affected by rheumatoid arthritis. Variations in the relative degrees of inflammation and fibrosis which might be interpreted as indicative of activity and healing, respectively, were seen in eight joints. Similar variations were seen also in adjacent blocks taken from the same region of joints and occasionally in a single section.

4. Minor variations in the degree of inflammation and fibrosis were seen in one joint affected by gout, two by rheumatic fever and two by systemic lupus erythematosus.

5. These variations in histopathology, were not related to treatment with gold or other drugs, but occurred naturally in the course of the disease. Caution must be exercised in attributing/

attributing to drugs (e.g., cortisone and ACTH) changes which occur naturally in the synovial tissue in the course of rheumatic diseases.

SECTION III.

The diagnostic Value of Histological Examination of Subcutaneous Nodules in Rheumatoid Arthritis, with particular reference to their differentiation from Granuloma Annulare.

INTRODUCTION.

The literature up to 1938 on rheumatic and other subcutaneous nodules was reviewed and discussed by Keil (1938) in a lengthy monograph. This author mentioned the following conditions in the differential diagnosis of nodules associated with rheumatic disease :- rheumatoid arthritis, granuloma annulare, gout, rheumatic fever, polyarteritis nodosa, subcutaneous nodules with the histological features of those found in rheumatoid arthritis or rheumatic fever but without other evidence of either disease, syphilis, erythema elevatum diutinum and fibrositis. He concluded that these different nodules could be differentiated from one another but devoted only a short section of his article, based entirely on reference to previous papers, to the relationship between rheumatoid arthritis and granuloma annulare. Reports which have appeared on this subject since have been very limited in their scope. The main object of this section of the thesis is to compare the/

the histological findings in rheumatoid arthritis with those in granuloma annulare in a larger series than has been observed hitherto. It will be shown that a definite diagnosis can be made in most cases. The occurrence in cases of rheumatoid arthritis and rheumatic fever of nodules unconnected with those diseases led to a comparison of the lesions of those diseases with other nodules such as foreign body granulomata, dermoid cysts and traumatic nodules. Observations have been made upon all the conditions listed by Keil except the last two. The literature will be reviewed in the order given above dealing mainly with articles published since Keil's monograph.

Prior to 1938, lesions of the histological pattern of the subcutaneous nodule of rheumatoid arthritis* had been described only in the subcutaneous tissue. Since then lesions of identical histological pattern have been described in many situations. Their occurrence in synovial tissue has been referred to and illustrated in Section I of this thesis (Bennett et alii, 1940 ; Kersley and Gibson, 1952 ; Cases 20 & 33 of this study - Fig. 13, p. 23). They have been described also in abdominal connective tissue, the larynx, pleura, skeletal muscle and spleen (Raven et alii, 1948) and/

* For convenience lesions of this structure will be referred to as " rheumatoid nodules " whether they occur in subcutaneous tissue or other sites.

and in the heart (Bennett et alii, 1940 ; Baggenstoss and Rosenborg, 1944 ; Gruenwald, 1948; Raven et alii, 1948 ; Bywaters, 1950) (See Section VI). The ocular lesion which occurs in some cases of rheumatoid arthritis and is known variously as episcleritis (Smoleroff, 1943), brawny scleritis (Derby, 1916) and scleromalacia perforans (Verhoeff and King, 1938) has the same structure as the subcutaneous nodule as these three papers showed.

There have been several reports of the occurrence of cholesterol in rheumatoid nodules during the last thirteen years (Layani, 1939 ; Weber, 1943, 1944-5 ; Fletcher, 1946; Kersley et alii, 1946 ; Raven et alii, 1948; Collins, 1949 (e) ; Horwitz, 1949 (b)). Some of these authors regarded cholesterol-containing nodules as a rarity and a special type (Weber, Fletcher, Raven et alii) whereas others found cholesterol frequently in nodules of long duration (Kersley et alii, Collins, Horwitz). Russell (quoted by Raven et alii) noted that the incidence of sudanophilic substances in these nodules was no greater than in any lesion with central necrosis. In a recent publication, Fletcher (1951(b)) regarded lipoid deposition as the final stage of the rheumatoid nodule. Calcification in the centre of some older nodules was mentioned by Bennett et alii (1940) and by Horwitz, (1949 (a)) whereas Collins (1949 (f)) stated that it does not occur

and/

and Rosenberg (1949) that it is very rare.

Keil regarded the nodules which occur in cases of juvenile rheumatoid arthritis as having the same structure as those of adult rheumatoid arthritis, a view which was shared by Paterson (1919-20), Coates and Coombs, 1926, Findlay (1931) and Bennett et alii (1940). On the other hand Debre and Uhry (1931), Schlesinger (1938) and Bywaters (1951) thought that nodules in juvenile rheumatoid arthritis bear a closer histological resemblance to those of rheumatic fever than to those of adult rheumatoid arthritis. One of the nodules studied by Collins (1937) was removed from a case of " Felty's Syndrome " but had a histological structure identical with those from typical rheumatoid arthritis. Hench and Rosenberg (1944) described the histology of a subcutaneous nodule occurring in a case of "palindromic rheumatism " as differing from that of rheumatoid arthritis, particularly in the absence of necrosis. There is considerable doubt about the classification of this syndrome, Hench and his colleagues (Hench and Rosenberg, 1944 ; Hench 1947) and Weber (1946) regarding it as an entity, whereas other authorities (Ropes and Bauer, 1945 ; Bywaters, 1949; Collins, 1949 (g) ; Fletcher, 1951(c)) consider it to be a variant of rheumatoid arthritis.

Several reports have appeared since the introduction of cortisone and ACTH, some of which attributed/

attributed changes in nodules to the use of these hormones. Rosenberg (1951) stated that they regularly decreased in size during cortisone therapy but did not disappear. Some nodules which had responded to treatment enlarged following cessation. No mention was made of histological studies. Norcross et alii (1950), Mundy et alii (1951), Hunt and Blanchard (1951) and Fienberg and Colpoys (1951) have carried out histological studies on nodules removed before and during or after therapy. The first two groups of writers saw no significant differences, whereas the other two groups saw definite changes, particularly in the intermediate zone, following treatment.

The histology of the cutaneous lesions of granuloma annulare was described many years ago (See Little, 1908) and was well reviewed by Goodman and Ketron (1936) on the basis of material from 12 cases. These authors worked out a sequence of changes, commencing with degeneration of"the connective tissue"in the skin. Kyrle (quoted by Keil) had previously regarded degeneration as the primary lesion in this condition. Goodman and Ketron noted that there was a marked resemblance between the late stages of granuloma annulare and rheumatoid nodules but noted that "hyperplastic occlusive changes in the blood vessels" occurred only in the latter. No study of rheumatoid nodules was made by these workers. Collins (1939) referred briefly to the histological/

histological resemblance between the two conditions, but does not appear to have studied granuloma annulare in detail. Prunty and Montgomery (1942) stated that granuloma annulare has a typical clinical and histological picture and gave a detailed differentiation from rheumatoid nodules, but they do not appear to have studied the latter. Bolgert (1944) described one definite and four doubtful cases of granuloma annulare and claimed that the histology of that condition and of rheumatoid nodules was identical with that of the juxta-articular nodules of syphilis. Bowers (1949) described and illustrated, one case each of granuloma annulare and rheumatoid arthritis and then gave details by which the two conditions could be differentiated.

The relationship between granuloma annulare and rheumatoid nodules is further complicated by records of the rare occurrence of the former in subcutaneous tissue rather than in the dermis. Some of these reports dealt only with clinical descriptions of cases in which typical skin lesions of granuloma annulare were associated with subcutaneous nodules in the absence of rheumatic disease (Gray, 1914; Ornstein, 1923; Goldschmidt, 1925 ; Raven et alii, 1948). The histology of subcutaneous nodules accompanying granuloma annulare was described by Grauer (1934) and Tizard (1948)/

(1948) in single cases as the same as that of the cutaneous lesions. Bywaters (1949) referred to the lesions in four cases of this type as being distinguishable with difficulty from those of rheumatoid nodules. Some authors have regarded subcutaneous granuloma annulare as rheumatoid nodules (Goodman and Ketron, 1936).

Subcutaneous nodules in other rheumatic diseases have been studied less intensively than rheumatoid nodules since 1938. The occurrence of nodules in ankylosing spondylitis was mentioned briefly by Lucchesi and Lucchesi (1947) and by Collins (1949 (h)), neither of whom gave any details of histological appearances. This is unfortunate for no other reference could be found to the occurrence of nodules in spondylitis. Indeed most authorities have not seen them. It is perhaps significant that both the writers mentioned subscribe to the belief that ankylosing spondylitis is a variant of rheumatoid arthritis and Collins noted that nodules occur mainly in cases of spondylitis with involvement of peripheral joints. Reasons for regarding spondylitis as a separate disease are given in Section I of this thesis (p. 75). No nodules from spondylitis were encountered in the present work.

Although most writers prior to 1938 emphasised the similarities between the subcutaneous nodules of rheumatic fever and rheumatoid arthritis (Coates and Coombs, 1926 ; Dawson, 1933; Dawson and Boots, 1933/

1933; Poynton, 1936), some had stated that they could be differentiated (Collins, 1937). Keil and subsequent authorities (Hawthorne, 1938 ; Bennett et alii, 1940 ; Bennett, 1943 ; Gibson, 1948; Bywaters, 1949; Collins, 1949 (i) ; Rosenberg, 1949) agreed with this opinion. Bennett's opinion that the subcutaneous nodule is the most characteristic single lesion in rheumatoid arthritis was based on a study of over 90 nodules from that disease and 42 from rheumatic fever. Poynton (1938), in discussing the interrelationship of rheumatic fever and rheumatoid arthritis mentioned a patient with severe rheumatoid arthritis and established mitral stenosis who, at the age of 60, developed numerous small nodules " precisely resembling those seen in children's rheumatism." No histological study was made by Poynton but a study of sections from similar cases by Bywaters (1949) revealed the features of rheumatoid nodules, rather than those of rheumatic fever.

Keil reviewed several papers in which were described nodules having features of like those found in rheumatic fever or rheumatoid arthritis in the absence of either disease. Thus Carpenter (1900-1) described a child of 17 months with numerous subcutaneous nodules arising from extensor tendons over joints of fingers, on the right great toe and on the scalp. Further nodules developed over many joints during the next year but at no time/

time were there any signs of rheumatic disease and the child does not appear to have suffered from granuloma annulare. The histological appearance of one of the nodules was described as "fibronuclear tissue." Carpenter referred to three other cases of nodules without rheumatism and in a later paper (1908) he described a fifth and illustrated the histological lesion which does not closely resemble any rheumatic nodule. In two other papers quoted by Keil - Hodge (1914) and Paterson (1919-20) - there was no mention of histology. In a fourth - Middleton (1887) - the patient had a definite history of rheumatic fever prior to the development of nodules.

Although these cases are not acceptable as examples of rheumatic nodules without rheumatic disease there are a few authentic cases of this type on record. Findlay (1931) described a child of 7 with numerous tender swellings on the dorsum of the left foot and a history of similar swellings on the right foot. The only previous illnesses were measles and a sore throat, there being no evidence of rheumatic disease. The description and illustration of a nodule are identical with the appearances in rheumatoid arthritis. Ten months later the nodules were in the same state and no further features had developed. Klinge (1933(d)) described four patients with nodules having the histology of rheumatoid nodules but no other rheumatic stigmata. The duration of follow-up was not/

not stated. More recently Bergstrand (1944) has described nine cases of " rheumatic nodules without rheumatism." Histological examination was carried out in all cases. Several of the patients appeared to be suffering from granuloma annulare, not rheumatoid arthritis - the lesions were described as ring-shaped - but in three at least this diagnosis can be excluded. These nodules had been present for at least a year without any other rheumatic features.

Although Bolgert (1944) compared the lesions of granuloma annulare and rheumatoid arthritis were identical with those of juxta-articular nodules of syphilis, most writers on the latter subject described a distinct lesion. There is some confusion in terminology which appears to be due to the use of different terms for different types of the same lesion (Kalz and Newton, 1943). The lesion described as " chronic fibroid subcutaneous syphilomata " (Weber, 1920), " nodosités juxta-articulaires " (Jeanselme and Eliascheff, 1926) and " subcutaneous nodules of juxta-articular type" (Hopkins, 1931) were all gummata showing varying degrees of inflammation, necrosis and fibrosis. Similar lesions have been described in yaws (Hudson, 1934-5). Klinge (1932) referred to the superficial resemblance between the rheumatoid nodule and the lesions of tuberculosis and syphilis (gummata) but regarded them all as distinguishable from one another.

MATERIAL /

MATERIAL AND METHOD.

Fifty one subcutaneous or cutaneous nodules from 45 cases of rheumatoid arthritis have been studied including a single nodule from one case of juvenile rheumatoid arthritis (Case 104), two cases of "Felty's Syndrome" (Cases 60 and 88), one each of psoriatic arthritis (Case 97) and "palindromic rheumatism." (Case 93) Twenty of these were removed personally by the writer at the Rheumatic Unit, Northern General Hospital. The biopsies were performed under local anaesthesia with 2% procaine, care being taken to avoid infiltrating the nodule itself. The remaining nodules were obtained at autopsy (six examples) or from the files of the Pathology Department. Thirty-eight of the nodules were situated in the elbow region, seven over metacarpo-phalangeal or interphalangeal joints, three on the knee, one on the wrist and one over mid-thoracic vertebrae. The site of the remaining nodule is not known. Lesions having the same structure as the subcutaneous nodules were also studied in the skin (Case 83), synovial tissue (Cases 20 and 33), bursae (Cases 61 and 62 - two bursae from the elbow in each case), the pharyngeal region (Case 1) and the heart (Case 2 - See Section VI).

Ten biopsies from nine cases of granuloma annulare were available in the files of the Skin Department, Royal Infirmary of Edinburgh. In all cases/

cases the clinical appearances were characteristic. Two biopsies from a tenth case were kindly made available by Dr. Agnes Macgregor, Pathologist to The Royal Hospital for Sick Children, Edinburgh and the case notes from this patient were abstracted by courtesy of Professor R.W.B. Ellis.

Subcutaneous nodules from other rheumatic diseases which were studied included single tophi from two cases of gout, seven nodules from five cases of rheumatic fever (three of these were obtained at biopsy by the writer) and single nodules from three cases of polyarteritis nodosa.

The following non-rheumatic lesions were studied :-

a) four subcutaneous nodules showing pathological features indistinguishable from those of rheumatoid arthritis, in the absence of rheumatic disease or granuloma annulare,
b) single nodules from one case/of each of syphilis and yaws,
c) forty tuberculous lymph nodes and one tuberculoma of the liver,
d) thirty-three foreign-body granulomata, three of these being removed from cases of rheumatoid arthritis by the writer,
e) twenty-two inclusion dermoid cysts,
f) two traumatic nodules and
g) a subcutaneous xanthoma removed from a case of rheumatic fever by the writer and a benign giant-cell synovioma from a case of rheumatoid/

rheumatoid arthritis.

The tissue was fixed in Zenker-formol or corrosive-formol, dehydrated, embedded in paraffin, sectioned and stained with haematoxylin and eosin. In some cases serial sections were studied : in others extra stains were used, such as Masson's trichrome, silver nitrate for calcium (Kossa's method), the Feulgen technique for nucleic acids, the Prussian blue reaction for iron, Congo-red for amyloid (on formalin-fixed frozen sections), Foot's reticulin stain and muci-carmine.

RESULTS.

Rheumatoid Arthritis.

Most of the nodules had the structure usually considered as characteristic, that is one or more foci of necrosis separated from vascular connective tissue by a layer of proliferating mesenchymal cells. In addition to this "fully developed" stage other nodules consisted of, or contained, foci which were regarded as early and late stages. The details of the fully-developed foci will be considered first and then the variations therefrom described.

The necrotic centre of the foci consisted of granular eosinophilic material containing cellular debris, which was associated with diffuse basophilic staining varying in intensity with the number of cells present (Figs. 78-79). The necrotic area frequently/

Subcutaneous Nodule in Rheumatoid Arthritis.

Fig. 78. Case 76 x 50. One of many fully developed foci in a large nodule. The central necrotic area is dark-staining because of much nuclear debris and diffuse basophilia (See Fig. 80, p. 124). Note the well developed intermediate zone (See Figs. 84-86, pp. 127-128, for detailed structure thereof).

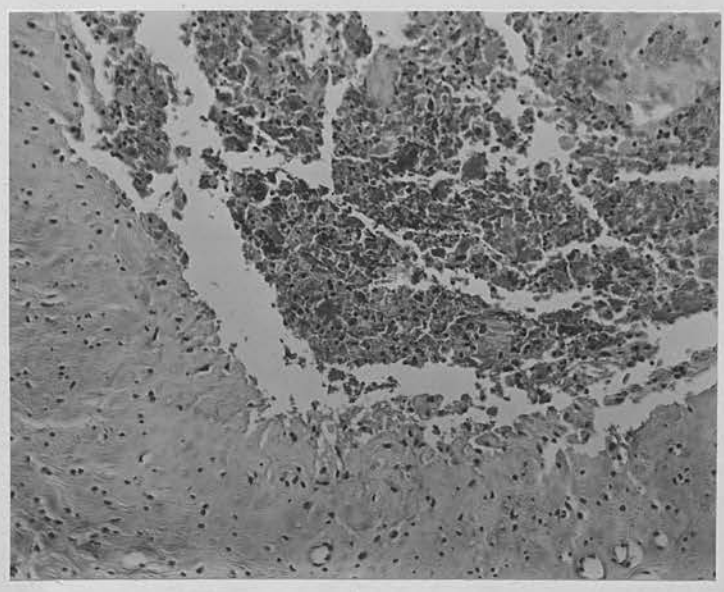

Fig. 79. Case 12 x 100. Much nuclear debris and diffuse basophilic staining of central zone. Poorly developed intermediate zone. The cleft is an artefact.

frequently measured 5 mm. - 1 cm. or more in diameter and was of highly irregular shape due to fusion of several foci. The basophilic material had a superficial resemblance to calcium deposits but gave no reaction with silver nitrate (Kóssa stain). On the contrary the fact that it reacted with the Feulgen technique (Fig. 80) indicated that it was of nuclear origin. In some nodules the necrotic material resembled amyloid when stained with haematoxylin and eosin but did not absorb Congo-red. The trichrome technique was found to be of limited value in determining the presence and state of collagen in these foci and in those of granuloma annulare. Collagen fibres which appeared healthy when stained with haematoxylin and eosin sometimes took the red of the trichrome, whereas obviously damaged collagen frequently stained green. The use of polarised light was found to be a more reliable method of determining the presence of healthy or damaged collagen. Healthy fibres were frequently found in the centre of foci, extending into and sometimes across the focus from neighbouring fibrous tissue (Figs. 81 and 82). Remains of blood vessels could be made out in 15 of the nodules.

The intermediate layer was usually complete in the smaller foci but was often incomplete in large foci (Figs. 78 and 95). It was usually avascular and the cells were arranged with their long axis radial to the necrotic centre and were so numerous that a definite palisade was regularly seen/

Subcutaneous Nodule in Rheumatoid Arthritis.

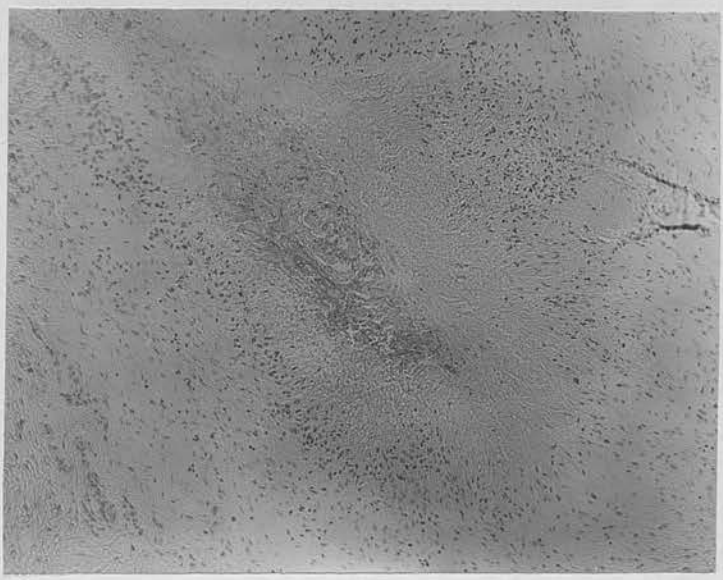

Fig. 80. Case 76 x 100. Slide treated by Feulgen technique for nucleic acids.
Same specimen as Fig. 78 showing presence of nuclei in central zone and that the diffuse basophilia is due to nuclear material.

Subcutaneous Nodule in Rheumatoid Arthritis.

Fig.81. Case 69 x 90. Part of a large focus showing necrotic central zone, intermediate layer and part of the outer zone. Note collagen fibres in the outer zone and a few in the intermediate layer which fade into the necrotic zone.

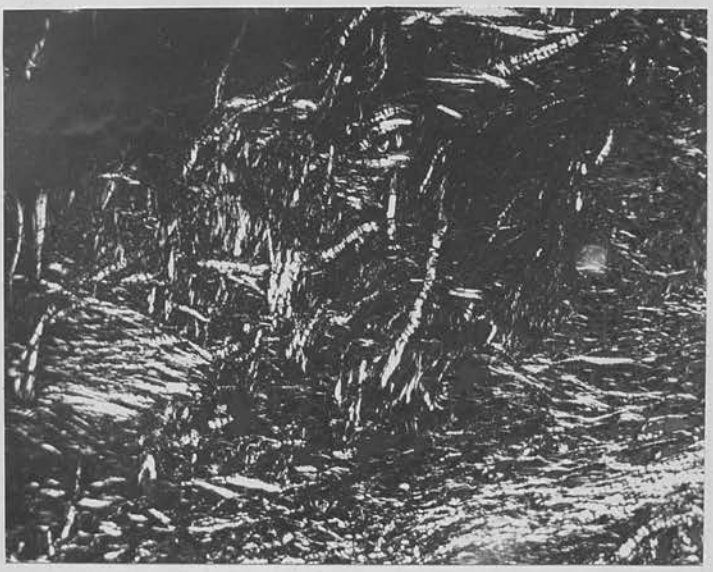

Fig. 82. Case 69 x 90. The same field photographed by polarised light. There are many fragments of collagen in the central zone. Elsewhere the continuity of such fragments with fibres in the outer zone was most striking.

seen (Figs. 83 and 84). This was by no means invariably present and was sometimes very poorly developed (Figs. 79 and 85). The predominant cell type was large and spindle-shaped, often identifiable as a fibroblast by the presence of collagen fibres merging with the necrotic centre (Figs. 83 and 84). Many of the cells were polyhedral rather than elongated and with basophilic cytoplasm suggesting histiocytes. Others could not be differentiated more accurately than as large mesenchymal cells. Multinucleate cells of all these types were present in 29 cases, many of them constituting small giant cells. This feature was most marked in the only cutaneous lesion studied (Case 83, Fig. 86). Mitotic figures were seen in 24 cases. Lymphocytes were present in 32 cases but were usually only in small numbers scattered among the large mesenchymal cells. They showed a distinct tendency to be more frequent in the outer part of this layer. Polymorphs were quite uncommon being present only in 13 cases and always in small numbers. Eosinophils were seen occasionally in 3 nodules.

The outer part of the foci and the intervening tissue consisted usually of cellular fibrous tissue containing many small blood vessels (Figs. 78 and 86). In 40 nodules these vessels were obviously newly formed, being of capillary size, lined with swollen endothelium around which lay large vasoformative cells. This vascular proliferation was

a/

Subcutaneous Nodule in Rheumatoid Arthritis.

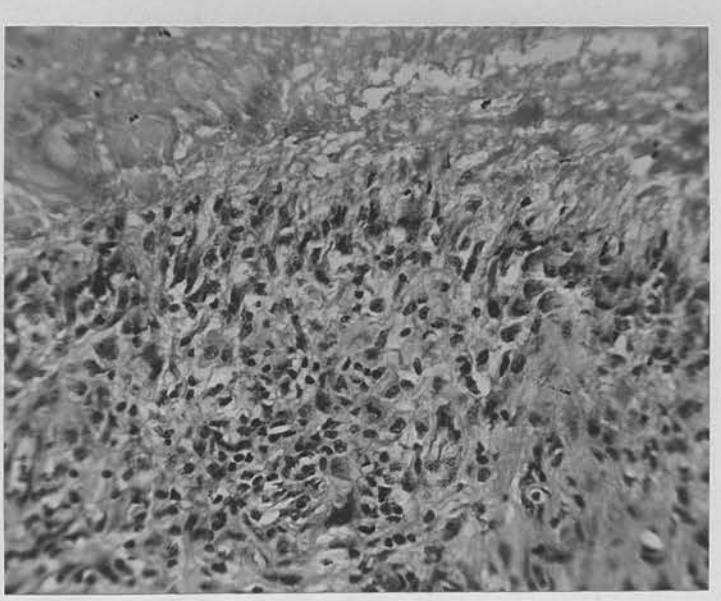

Fig. 83. Case 98 x 250. The necrotic central zone (top) is separated from the outer zone by a strip of fibroblasts and undifferentiated mesenchymal cells arranged radially. Many similar cells are seen in the outer zone, together with lymphocytes. See also Fig. 100, p. 138.

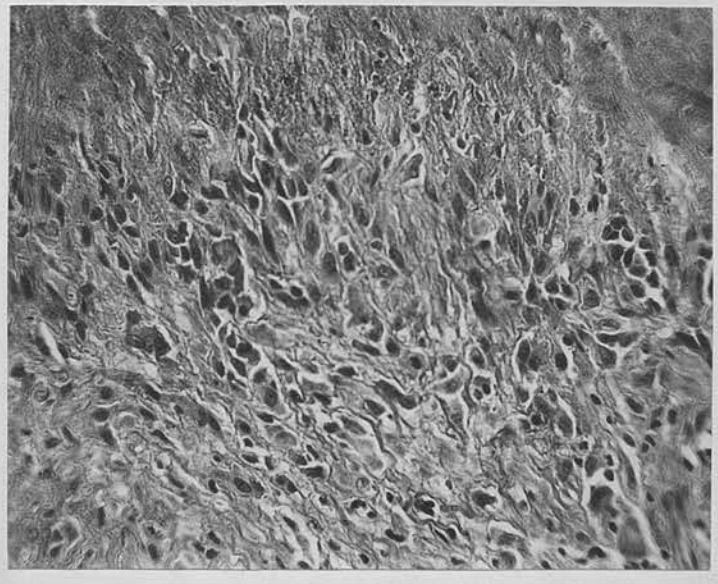

Fig. 84. Case 75 x 250. The intermediate layer of this nodule contains fine collagen fibres as well as fibroblasts, some of which are multinucleate.

Subcutaneous Nodule in Rheumatoid Arthritis.

Fig. 85. Case 70 x 50. The central zone here is very large, but the intermediate layer is poorly developed (lower centre). Marked perivascular cuffing is seen in the outer zone.

Cutaneous Nodule in Rheumatoid Arthritis.

Fig. 86. Case 83 x 100. Giant cells are unusually numerous in the intermediate layer. The nodule is otherwise " typical."

a marked feature in 18 of the fully developed nodules and in another 2 it was sufficiently predominant to produce an angiomatous appearance in much of the nodule (See P. 140). Arterioles and small arteries showed intimal fibrosis in 21 nodules (Fig. 87) and two instances each of subacute arteritis (Figs. 88- 93) and thrombosis were seen. Perivascular infiltration usually with lymphocytes was present in 30 cases and polymorphs, eosinophils and plasma cells were sometimes seen. These cells were also present diffusely throughout this zone in the same frequency. In two cases this outer zone spread into adjacent skeletal muscle.

The smallest foci seen did not show this zonal arrangement. They consisted instead of an accumulation of large mesenchymal cells with scattered lymphocytes (Fig. 94). Collagen fibres coursed between the cells, and were sometimes swollen or fragmented. Various foci which were transitional between this and the fully developed one were seen, basophilic staining being noted as soon as necrosis was present (Fig. 95).

Cholesterol clefts were present in the central zone of 12 nodules, and in the intermediate zone of seven of these. In some cases the foci were mainly of the fully developed type, those containing clefts being infrequent (Fig. 96), but in others they were a prominent feature (Fig. 97). Indeed, one nodule consisted mainly of hyaline fibrous tissue and cholesterol clefts/

Subcutaneous Nodule in Rheumatoid Arthritis.

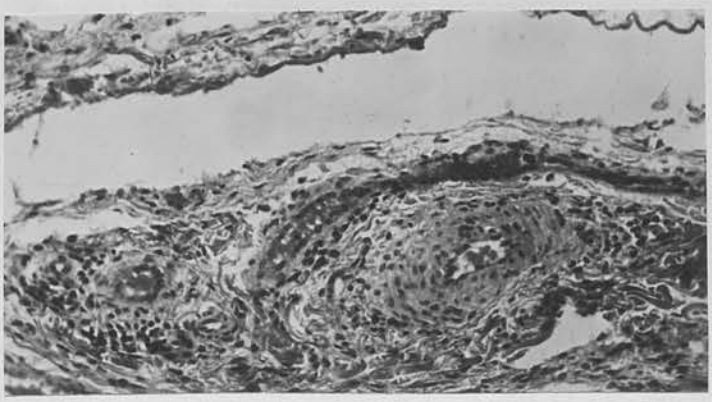

Fig. 87. Case 74 x 150.
Arteriole in outer zone showing cellular fibrosis of its wall. Endothelium of adjacent venule is swollen.

Subcutaneous Nodule in Rheumatoid Arthritis.

Figs. 88 to 93. Case 81 x 200.
The following six illustrations show the development of obliterative arteritis in the outer zone of a nodule. They are taken from sections of the same nodule cut at different levels, and all show the same vessel.

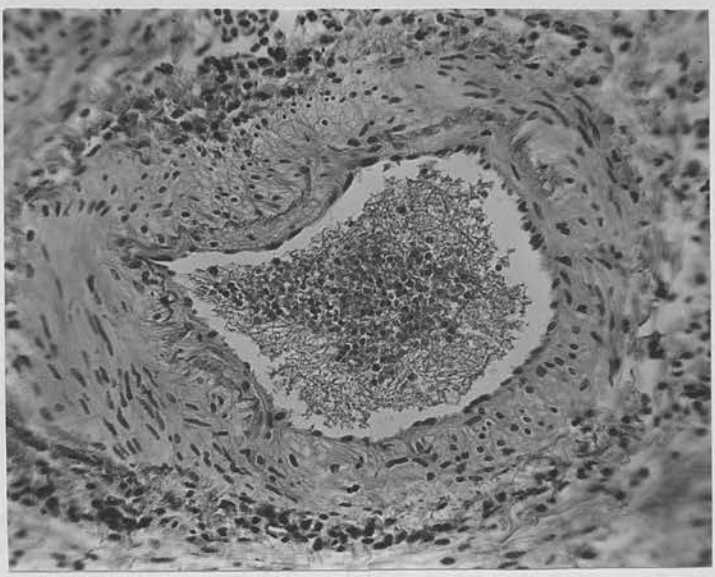

Fig. 88. Minimal fibrosis internal to the internal elastic lamina. Some disorganisation of the media. Lymphocytes in adventitia.

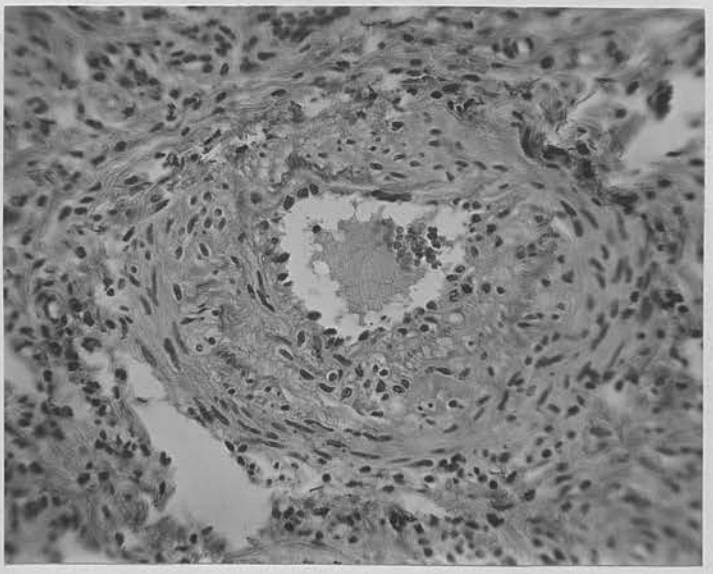

Fig. 89. More marked intimal thickening.

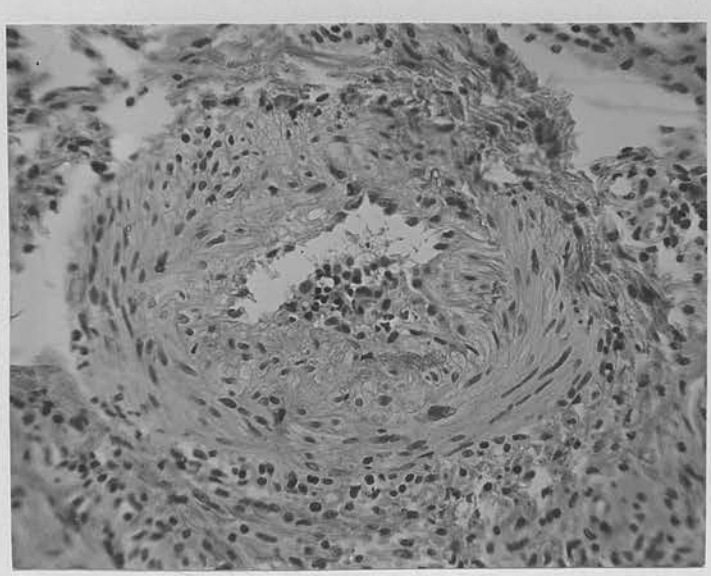

Fig. 90. Lymphocytic infiltration of thickened intima.

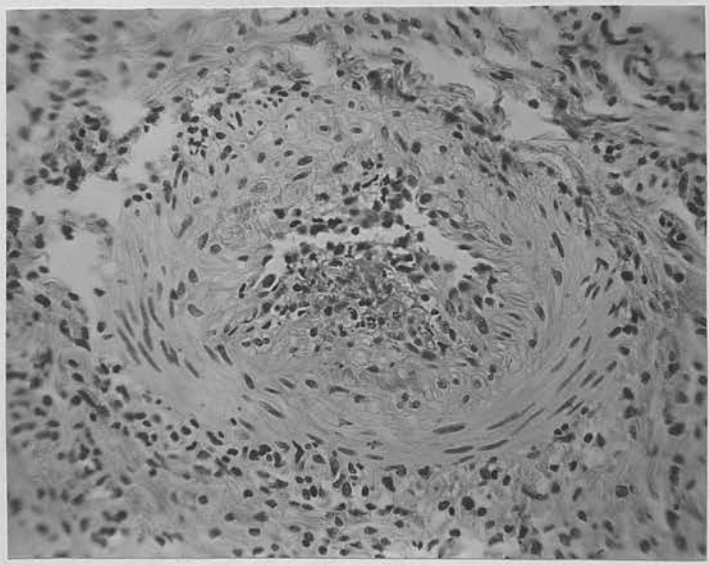

Fig. 91. Intimal infiltration more marked. Some fibrin also in the intima.

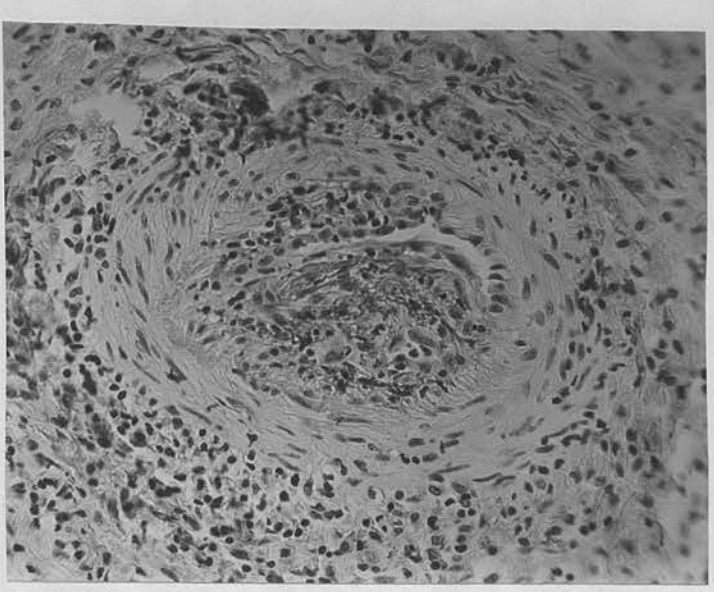

Fig. 92. Marked infiltration, still beneath intact endothelium. Adventitial infiltration more marked.

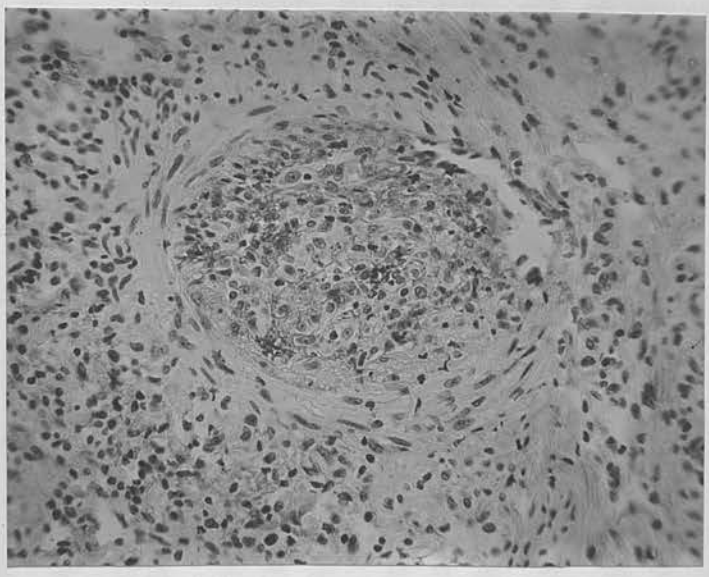

Fig. 93. Almost complete occlusion of lumen by cellular mass. Considerable disorganisation of media. Marked infiltration of adventitia.

Subcutaneous Nodule in Rheumatoid Arthritis.

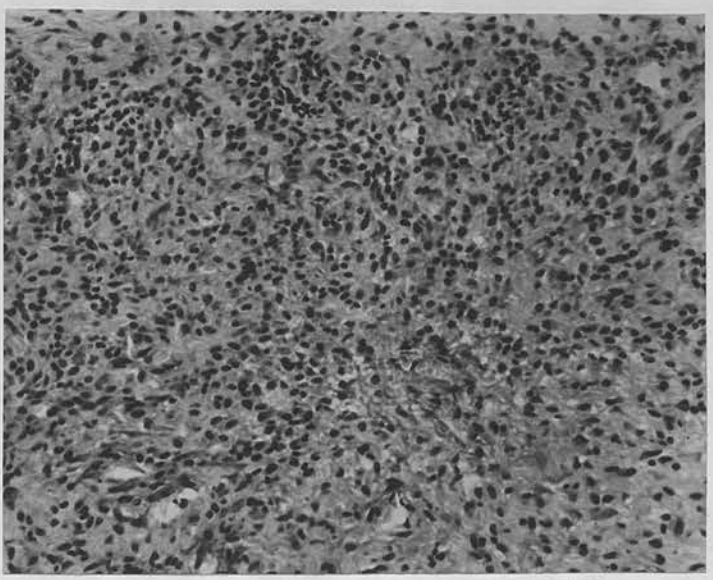

Fig. 94. Case 80 x 180. Focus of large mesenchymal cells and small numbers of lymphocytes which was the earliest stage seen. There is a little swelling and fragmentation of collagen (bottom right).

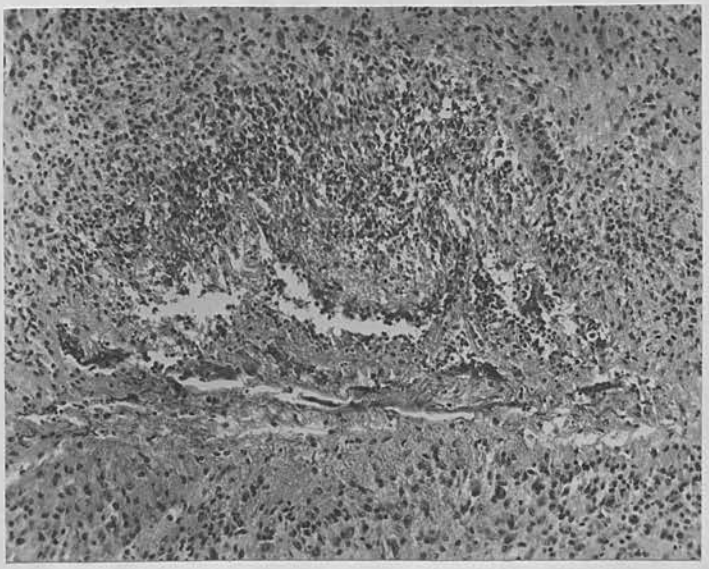

Fig. 95. Case 81 x 100. A small focus, combining the features of Fig. 94 with those of the fully developed lesion. The clefts are an artefact.

Subcutaneous Nodule in Rheumatoid Arthritis.

Figs. 96 and 97. Case 61 x 100.

Two foci containing cholesterol clefts and foamy histiocytes, Fig. 96 at a fairly early stage and Fig. 97 much later. Both foci were in the same nodule.

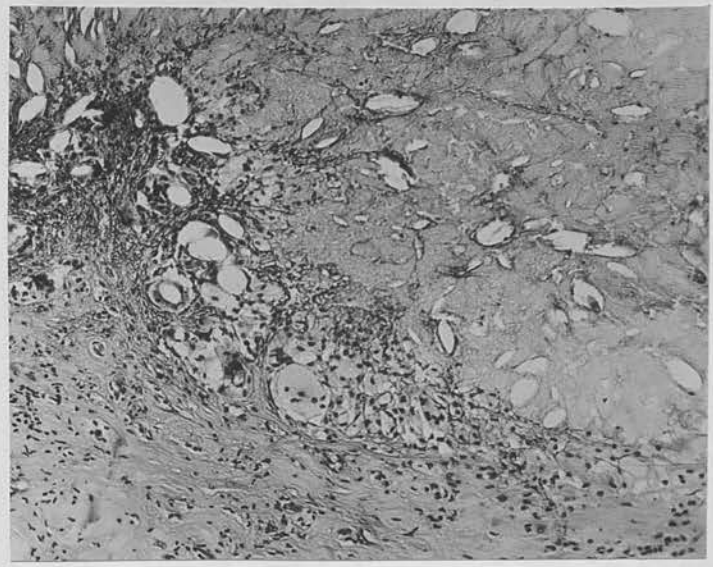

Fig. 96.

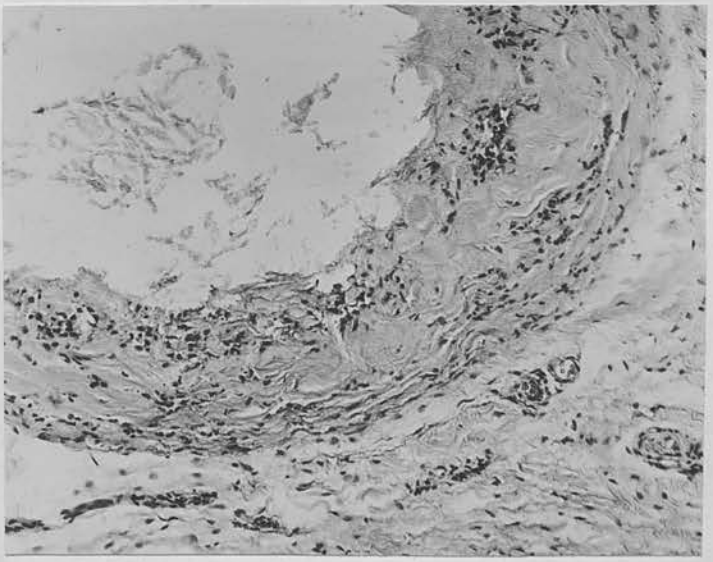

Fig. 97.

clefts with patches of cellular fibrous tissue containing newly formed capillaries (Fig. 98). Transitional stages between these extremes were seen either in different nodules or occasionally in one case. Cholesterol clefts were nearly always accompanied by varying numbers of foamy histiocytes but these were present in 6 cases in the absence of clefts (Fig. 99).

Another prominent feature of the rheumatoid nodules was cavitation of the necrotic zone sometimes accompanied by the formation of a definite bursal lining. It was sometimes difficult to be sure whether cavitation was an artefact (Fig. 79) but bursa-formation, which was seen in 8 nodules, was undoubtedly a true ' in vitam ' change (Fig. 100).

Appearances which were seen only occasionally were a) the presence of capillaries in the intermediate zone (10 nodules), giving the appearance of non-specific granulation tissue in one case (Fig. 101).

b) haemosiderin, seen only in one case.

c) concentrically arranged collagen fibres between the structureless central zone and the intermediate zone. These fibres were themselves necrotic suggesting that recurrent activity was taking place (Fig. 102).

d) hyaline change affecting all zones of some foci in a nodule, whereas other foci in the same nodule showed all three zones, a feature suggesting healing (Fig. 103).

e)/

Subcutaneous Nodule in Rheumatoid Arthritis.

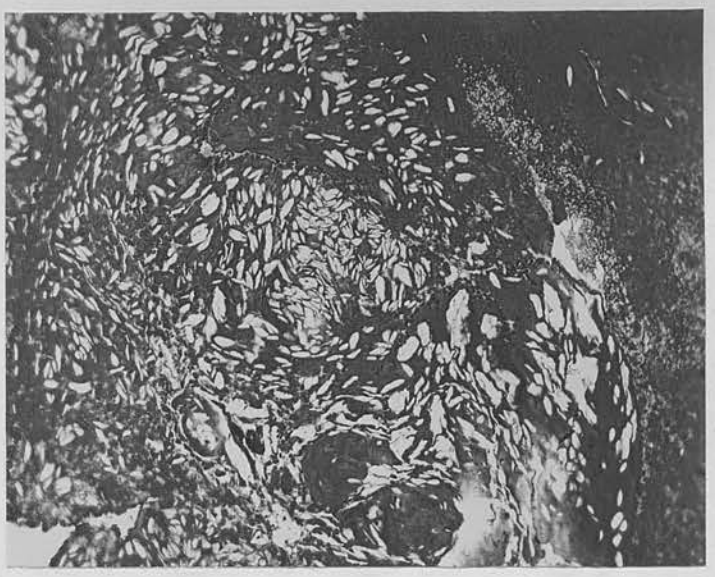

Fig. 98. Case 87 x 100. This nodule consisted mainly of cholesterol clefts lying in hyaline fibrous tissue.

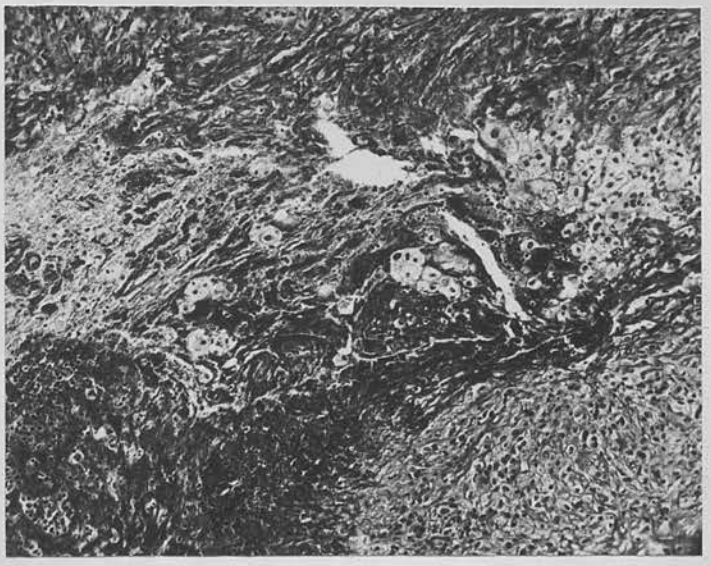

Fig. 99. Case 71 x 100. Masson's trichrome stain. Many foamy histiocytes in the central zone and intermediate layer of a nodule in which cholesterol clefts were not seen. The large spaces are an artefact.

Subcutaneous Nodule in Rheumatoid Arthritis.

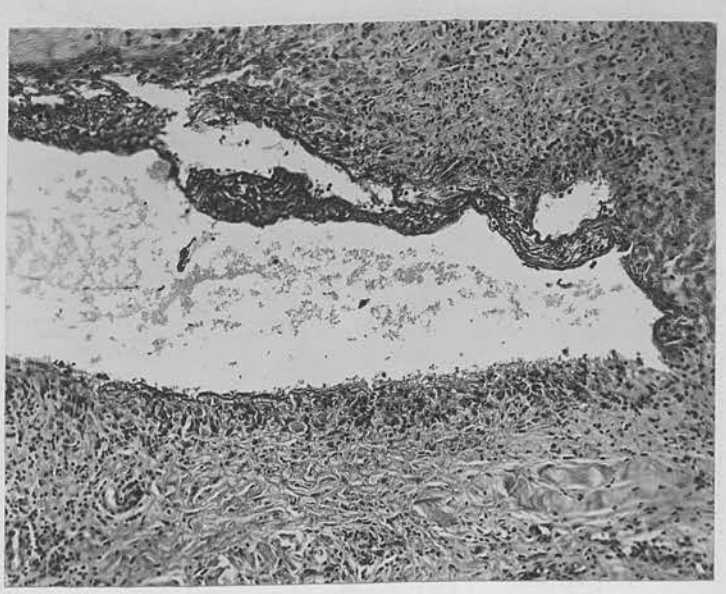

Fig. 100. Case 98 x 100. Liquefaction of the central zone has led to formation of an adventitious bursa, lined by the intermediate layer. See also Fig. 83, p. 127.

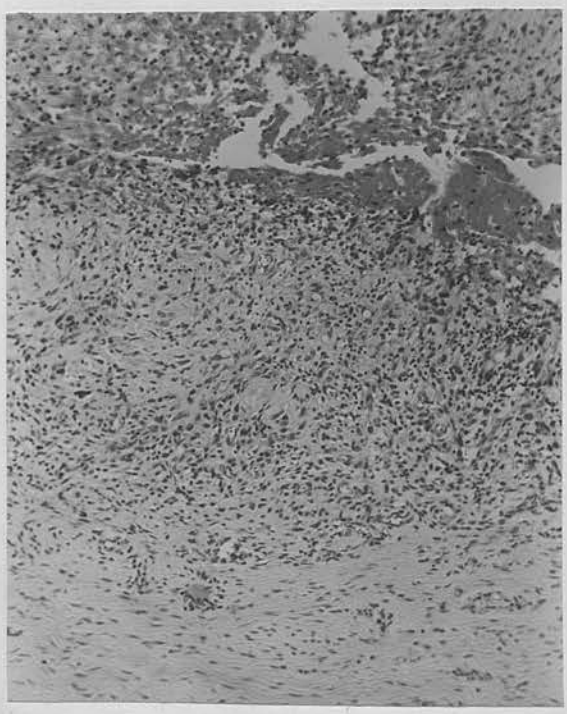

Fig. 101. Case 82 x 100. The intermediate zone here is unusually broad, lacks the radial arrangement and contains many capillaries and lymphocytes.

Subcutaneous Nodule in Rheumatoid Arthritis.

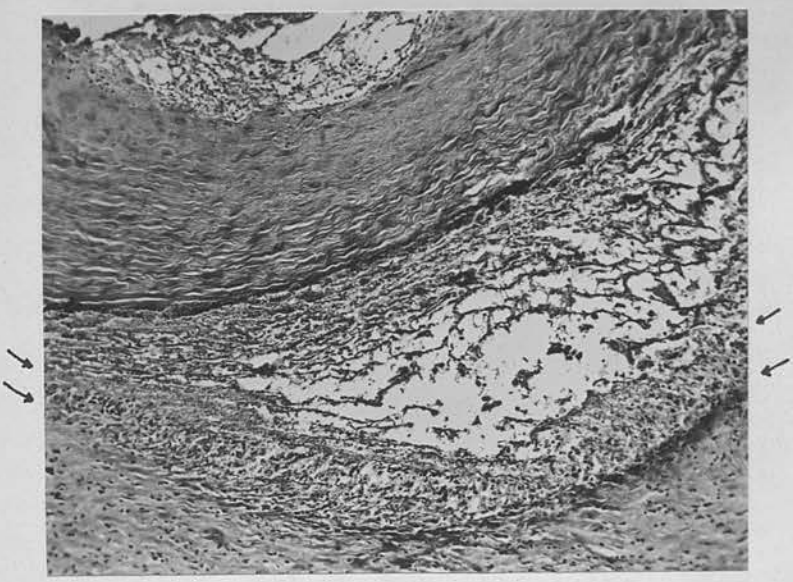

Fig. 102. Case 89 x 75. The intermediate zone is indicated by arrows. Within it are a zone of fibrinous infiltration, a zone of necrotic concentrically arranged collagen fibres and an amorphous necrotic zone.

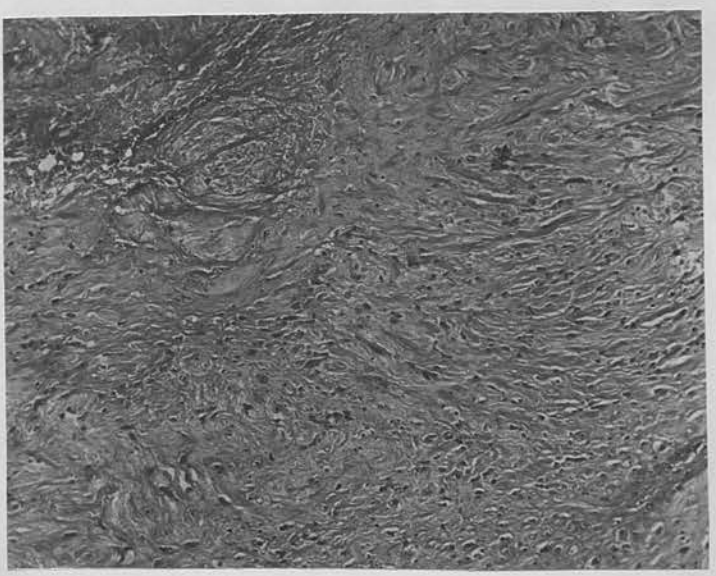

Fig. 103. Case 80 x 100. Very late stage with necrotic material (top left) surrounded by dense, hyaline fibrous tissue.

e) the nodule examined in juvenile rheumatoid arthritis lacked the marked zonal arrangement seen in adults. It consisted rather of loose inflammatory tissue in which patches of fibrin deposition and degeneration of cells occurred (Fig. 104).

f) the nodules from the two cases of " Felty's Syndrome" and that of psoriatic arthritis were in every way typical.

g) the nodule from the case of " palindromic rheumatism" was of particular interest. This patient, a man of 39, had suffered from recurrent transient effusions and pain in many joints for three years, his clinical features being the same as those described by Hench and Rosenberg (1944). For a few weeks prior to the biopsy there was permanent stiffness and slight swelling of the right wrist and several joints of the right hand. Radiological examination revealed soft tissue swelling only. The nodule, which was discovered during examination, was on the subcutaneous border of the right ulna. Histologically much of this nodule consisted of actively proliferating fibrous tissue containing very many newly-formed capillaries and had an angiomatous appearance (Fig. 105). Irregular necrotic areas were present, some bearing little resemblance to the usual rheumatoid nodule (Fig. 106), whereas others had a definite intermediate zone though the central area was atypical (Fig. 107).

The nodules in synovial tissue and bursae were

in/

Subcutaneous Nodule in Juvenile Rheumatoid Arthritis.

Fig. 104. Case 104 x 100. Much fibrin has been deposited around two arterioles and around this there is oedematous inflammatory tissue. Compare with Fig. 122, p.155.

Subcutaneous Nodule in " Palindromic Rheumatism "

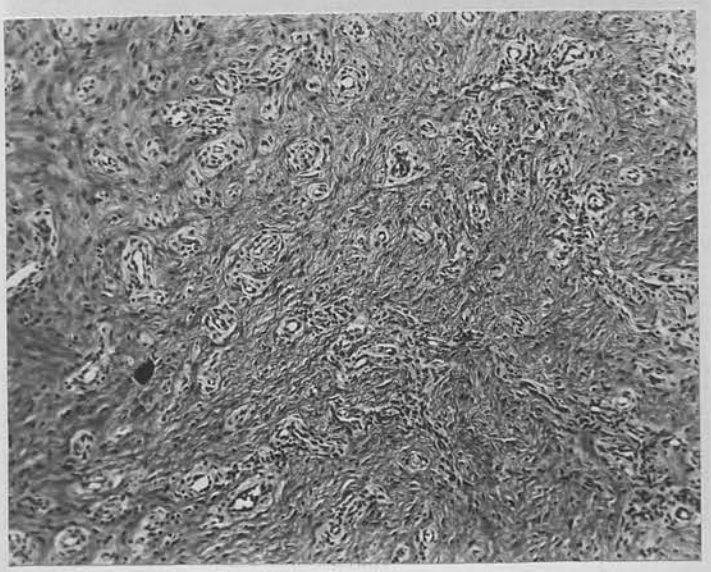

Fig. 105. Case 93. x 75. Cellular fibrous tissue containing many newly formed capillaries. This angioma-like tissue formed much of the nodule.

Subcutaneous Nodule in " Palindromic Rheumatism "

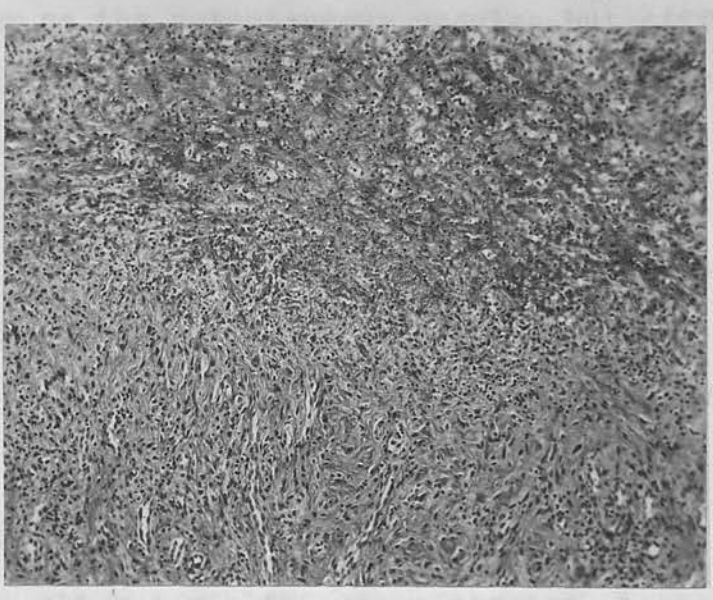

Fig. 106. Case 93 x 75. Another field showing similar vascular fibrous tissue (below) and a large patch of necrosis (above). There is polymorph infiltration of the necrotic patch but no intermediate layer.

Fig. 107. Case 93 x 50. Fragmented necrotic material (centre) is separated by a poorly developed intermediate layer from the surrounding tissue.

in every way characteristic. Those in the pharyngeal region and heart had the same zonal pattern as the subcutaneous nodules but differed slightly in the structure of these zones. Thus in the pharyngeal nodule the foci were typical (Fig. 108) but the surrounding tissue contained unusual numbers of polymorphs, and in the heart an unusually dense lymphocytic infiltration was seen in the outer part of the intermediate zone which also contained many "myocytes" (Figs. 230-234, pp. 342-344.

Granuloma Annulare.

In all but one of the cases studied lesions were confined to the skin. Multiple foci were present in most of the biopsies and most of them consisted of three zones as in rheumatoid arthritis.

The necrotic central zone was usually of the order of 550 x 400 μ or less in diameter, though in one case it measured 2140 x 370 μ. The foci were much less irregular in shape than in rheumatoid arthritis and few confluent foci were seen. As in rheumatoid arthritis the central zone consisted basically of granular eosinophilic material but there were two differences - cellular debris was an inconspicuous feature and basophilia was rarely seen (Figs. 109-112). As in rheumatoid arthritis refractile collagen fibres were seen in the centre of many foci, but were often fragmented. The remains of a small arteriole were seen in one case only. Cholesterol clefts were present in only one case and bursa formation was not seen.

The/

Pharyngeal Nodule in Rheumatoid Arthritis.

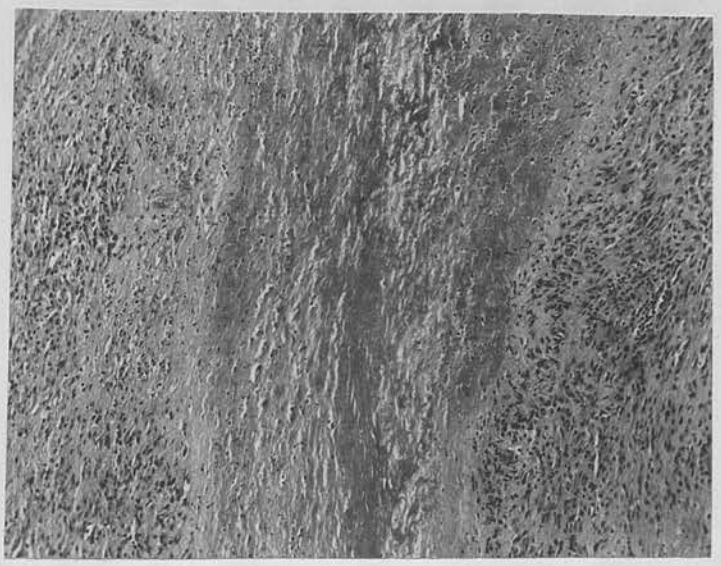

Fig. 108. Case 2 x 100. The usual zonal arrangement is seen in this retro-pharyngeal nodule. Unusual numbers of polymorphs, sometimes of focal arrangement, were seen in the outer zone.

Cutaneous Lesions in Granuloma Annulare.

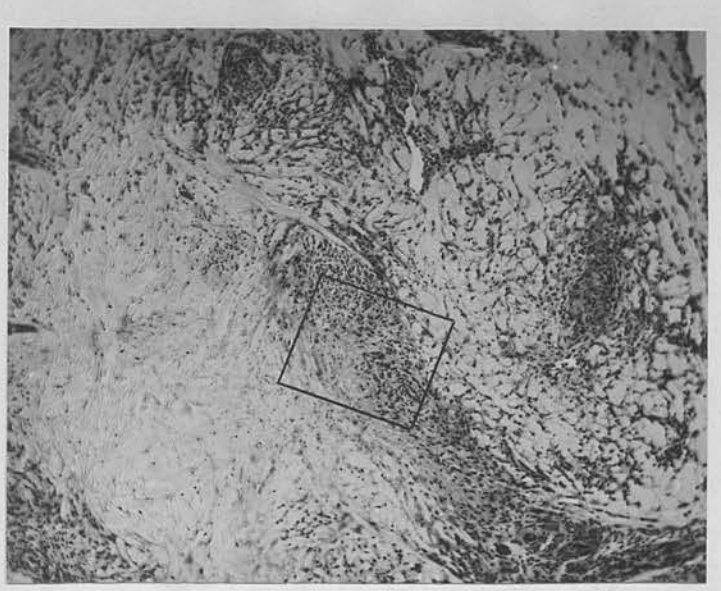

Fig. 109. Case 929 x 50. A focus of necrosis (left) is surrounded by an incomplete layer of inflammatory cells and small vessels. Vessels in adjacent fatty tissue are surrounded by similar cells. See also Fig. 113, p. 148.

Fig. 110. Case 926. x 100. A similar focus just under the epidermis. A few fragmented nuclei are seen in the central zone.

Cutaneous Lesions in Granuloma Annulare.

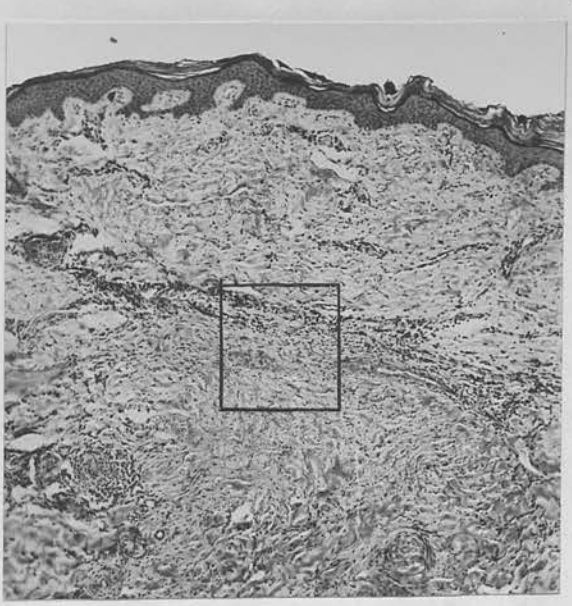

Fig. 111. Case 931. x 50. Another small focus with poorly developed intermediate zone. See also Fig. 114, p. 148.

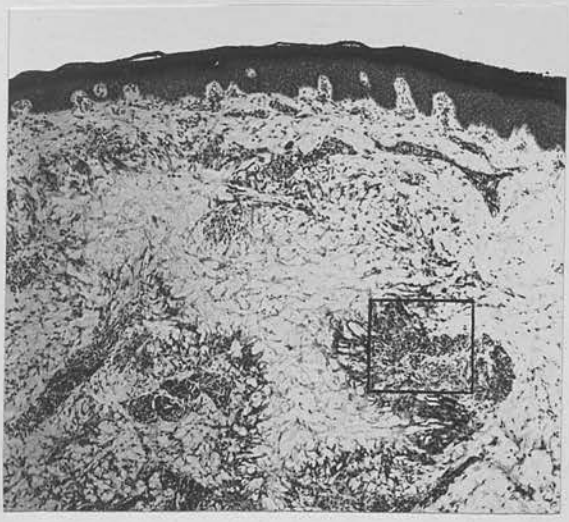

Fig. 112. Case 932. x 40. This was the largest and best developed focus seen in the ten cases. See also Figs. 115, p. 149 and 117, p. 151.

The intermediate zone was not complete in any of the foci and was very poorly developed even in fairly large foci (Figs. 109-112). Although there was a tendency towards radial orientation this was not so marked as in rheumatoid arthritis and the smaller number of cells in the zone gave rise to palisade formation of much less marked degree. Large mesenchymal cells were again predominant in most places but were not readily identifiable as fibroblasts (Fig. 113). Occasional binucleate forms were seen but no giant cells. Mitotic figures were noted in 1 case only. Lymphocytes were frequently seen throughout the zone, being always more numerous than in rheumatoid nodules (Fig.114) and the predominant cell in places (Fig. 115). Polymorphs were present in small numbers in 2 cases. Capillaries were quite frequent. Cholesterol clefts were not seen in this zone, nor was there any sign of foamy histiocytes.

The outer zone was less extensive and less well developed than in rheumatoid arthritis (Figs. 109, 111 and 112). Once again it consisted of cellular connective tissue containing diffusely scattered and perivascular lymphocytes, plasma cells and histiocystes. Vascular proliferation was much less marked than in the rheumatoid nodules and fibrosis of arterioles was minimal in degree and extent.

The smallest focus seen showed definite zonal arrangement (Fig. 116), suggesting that necrosis or degeneration preceded cellular proliferation or infiltration./

Cutaneous Lesions in Granuloma Annulare.

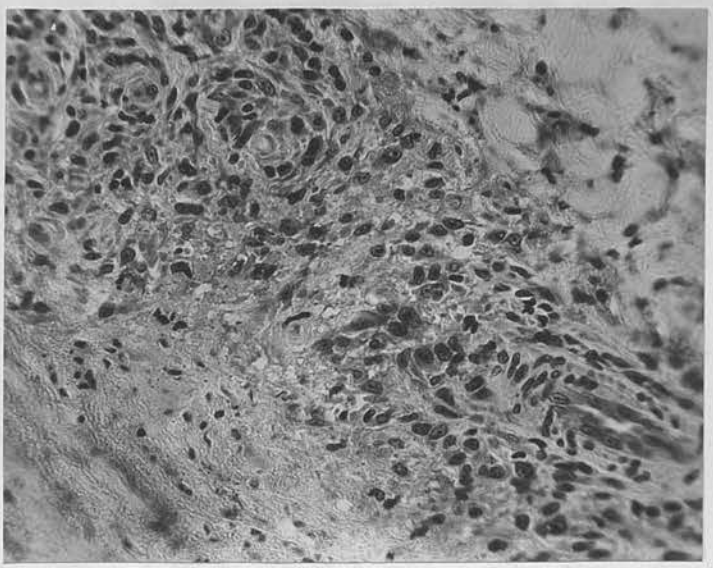

Fig. 113. Case 929 x 250. The field outlined in Fig. 109. The necrotic zone (bottom left) contains a few degenerate cells. It is separated from the adjacent fat by a layer in which large mesenchymal cells, lymphocytes and capillaries are seen.

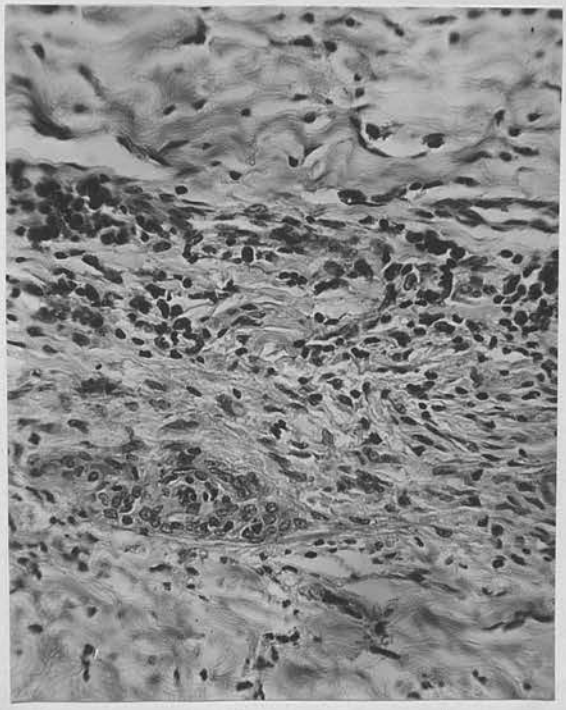

Fig. 114 Case 931 x 250. The field outlined in Fig. 111. The intermediate zone here has an inner part of fibroblasts and mesenchymal cells (below centre) and an outer part of lymphocytes (above centre).

Cutaneous lesions in Granuloma Annulare.

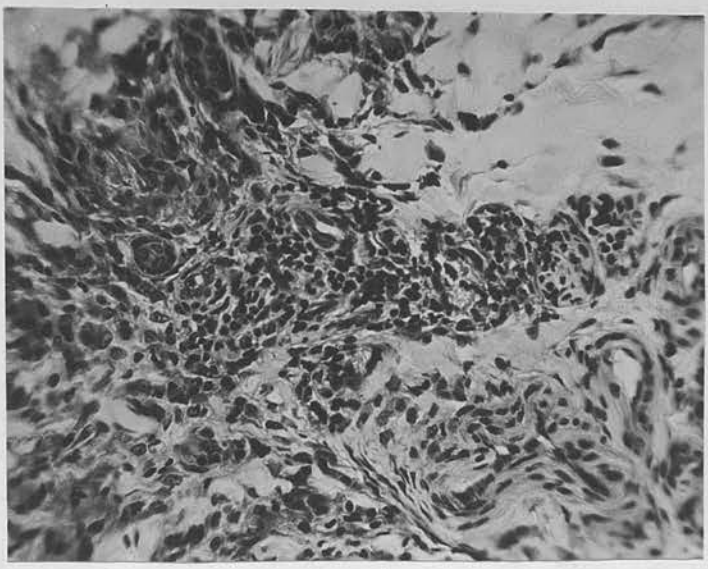

Fig. 115. Case 932 x 250. The field outlined in Fig. 112. The intermediate layer shows a tendency to radial arrangement in its inner half (left) but is more vascular and pleomorphic than in rheumatoid nodules.

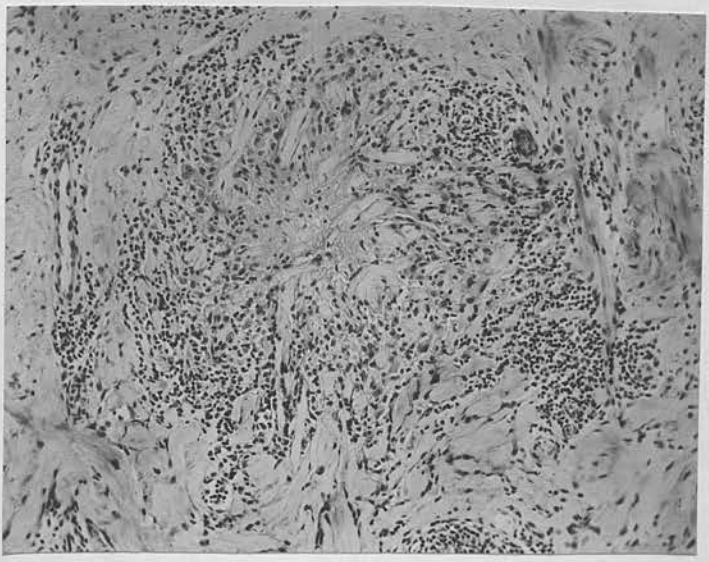

Fig. 116. Case 930 x 100. The smallest focus seen in the ten cases. Central necrosis is present and the surrounding cellular layer is loose. It contains large mesenchymal cells, many lymphocytes, some histiocytes and several capillaries.

infiltration.

In one case a large granulomatous area with many capillaries, large mesenchymal cells, and lymphocytes was found close to the largest focus seen in the series (Fig. 117).

The subcutaneous lesions were removed from a child aged 9. The condition had been present for 6 years, in the form of nodules " the size of melon seeds " on the dorsum of the right hand. Similar nodules had been present on the left hand for 3 years. There was no evidence of rheumatic disease, the B.S.R. being 3 mm. per hour and Xrays normal. Two nodules were removed, the first showing the same features as the cutaneous lesions already described (Fig. 118). In the second the intermediate zone was much better developed and was more like that seen in the rheumatoid nodule (Fig. 119).

Other Rheumatic Nodules.

The two tophi examined showed the characteristic features of that lesion, namely deposition of urate crystals producing a chronic inflammatory reaction with many foreign-body giant-cells grouped around the crystals (Figs. 120 and 121). Extensive calcification was present in one case.

The rheumatic fever nodules presented a much less marked zonal arrangement than either rheumatoid arthritis or granuloma annulare. The features were particularly/

Cutaneous Lesions in Granuloma Annulare.

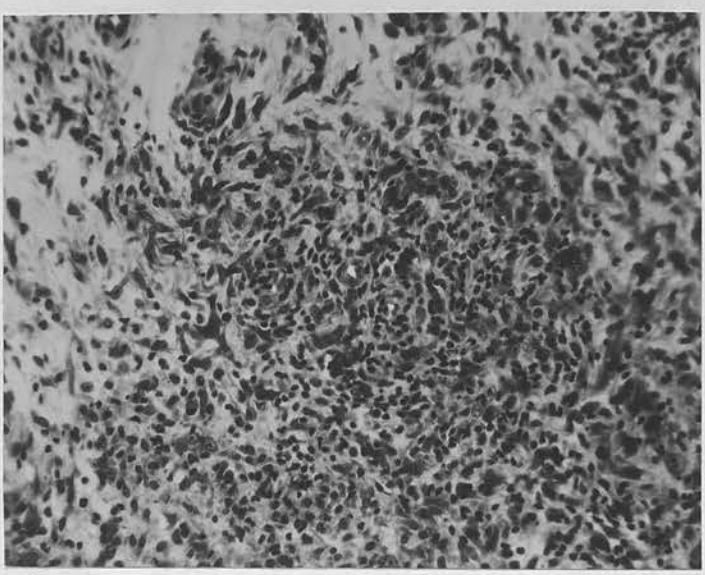

Fig. 117. Case 932 x 200. Granulomatous focus close to the lesion shown in Figs. 112 and 115.

Subcutaneous Lesions in Granuloma Annulare.

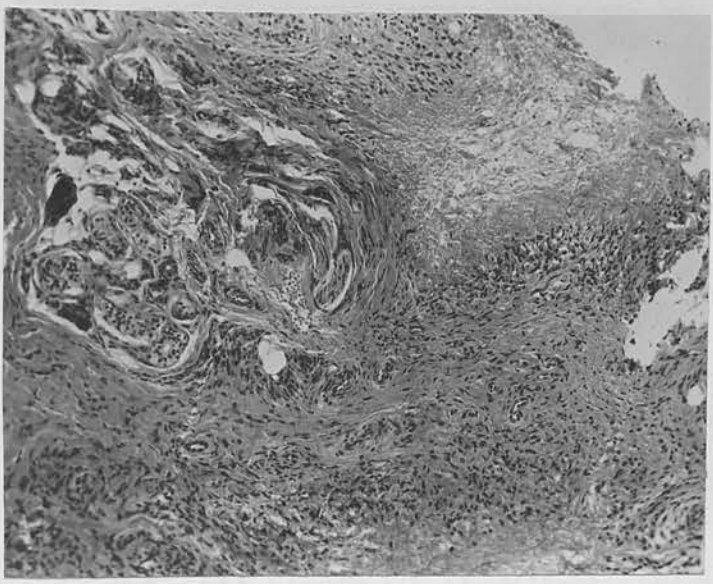

Fig. 118. Case 935 x 100. Parts of two foci are seen close to a group of sweat glands and a small nerve. These foci have the same structure as the cutaneous lesions, though the intermediate zone is a little more marked.

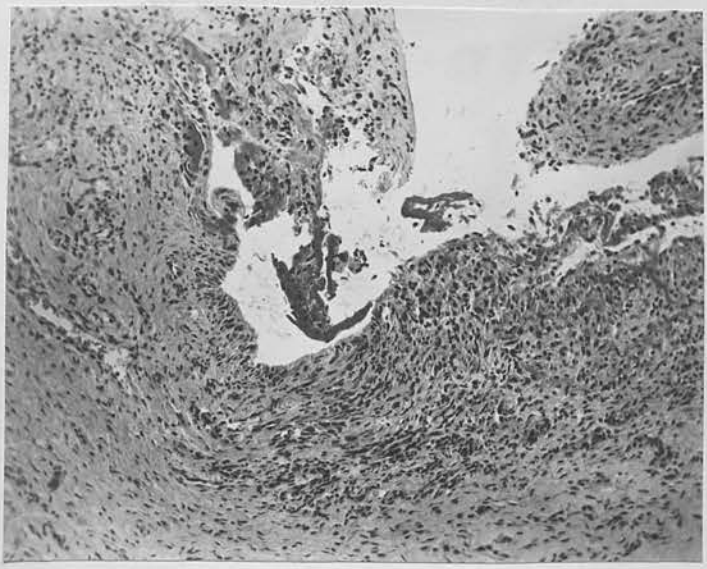

Fig. 119. Case 935 x
Another nodule removed three weeks later. Fragments of necrotic tissue are separated from cellular fibrous tissue by a definite layer of fibroblasts arranged radially.

Subcutaneous Nodule in Gout.

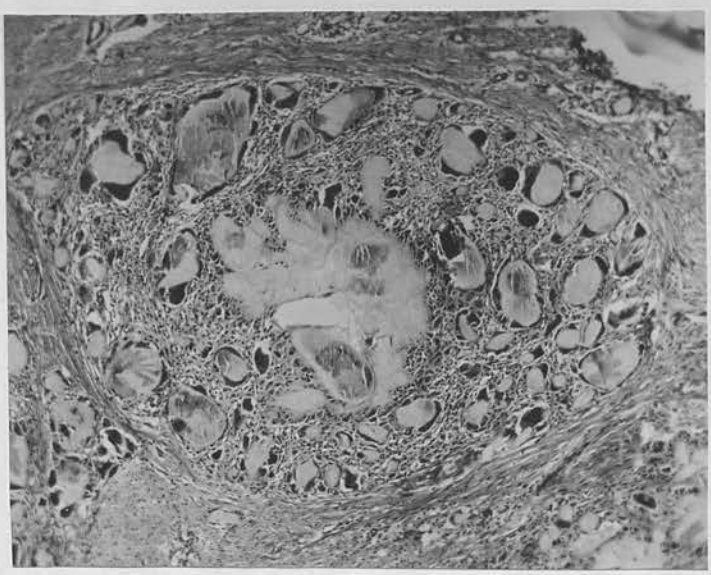

Fig. 120. Case 245 x 50. Urate crystals are surrounded by foreign body giant cells and vascular granulation tissue.

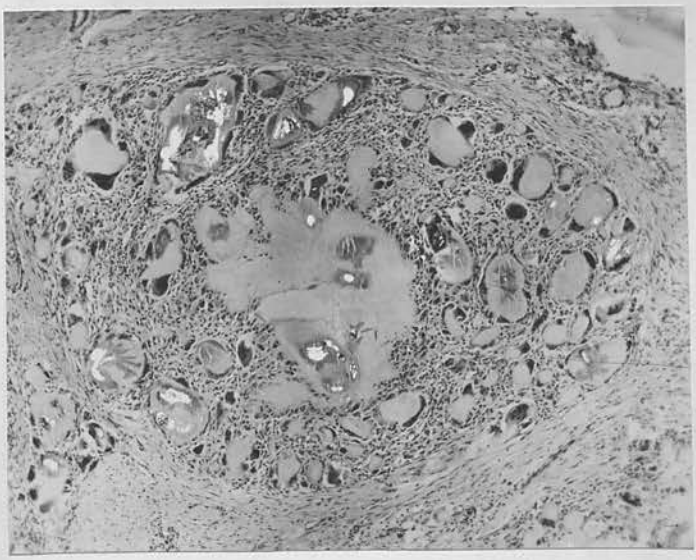

Fig. 121. Case 245 x 50. The same field photographed by polarised light.
The urate crystals are refractile. Many of them have disappeared because the tissue was fixed in an aqueous solution.

particularly well seen in one patient from whom two nodules were removed at two weeks and six weeks duration respectively (Case 257). The younger nodule consisted of proliferating connective tissue showing marked oedema, fibrin deposition and many newly formed capillaries (Fig. 122). Necrosis was fairly extensive but was not of focal distribution and the only evidence of an intermediate zone was a tiny clump of fibroblasts arranged radially with respect to necrotic tissue. The older nodule was very similar though the zones of necrosis were more defined (Fig. 123). Despite this no intermediate zone was seen, the necrotic tissue merging directly with the surrounding connective tissue . This was much more cellular than in the younger nodule and contained many fine collagen fibres (Fig.124). In another nodule a loose zone of degenerate collagen fibres and fibrin was surrounded by an irregular layer of fibroblasts and histiocytes with smaller numbers of lymphocytes and plasma cells. This layer lacked palisading and radial arrangement and was much less well-developed than in the rheumatoid nodules.

The lesions seen in polyarteritis nodosa differed entirely from the other nodules for they were vascular in situation. The characteristic features of acute necrotising arteritis were seen in one case (Fig. 125) whereas in the other two the lesions were at a later stage showing organisation. The vessels affected varied from small muscular arteries to arterioles.

Subcutaneous Nodule in Rheumatic Fever.

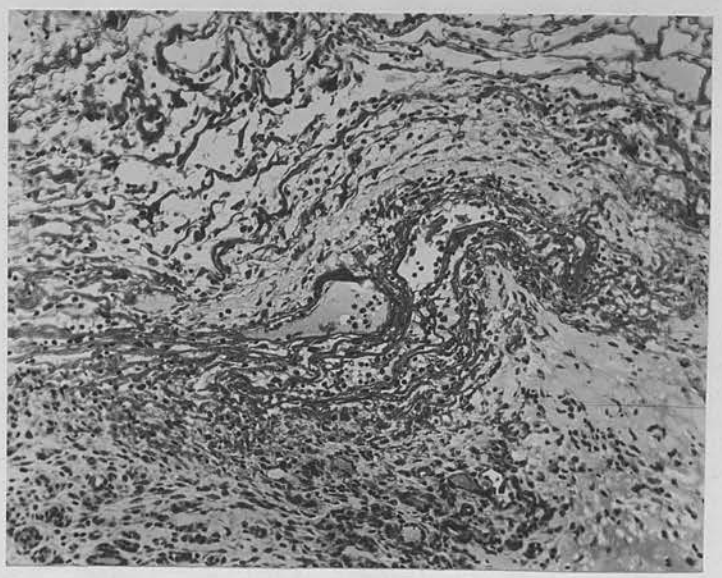

Fig. 122. Case 257 x 100. Nodule of two weeks' duration. Oedema, marked fibrin deposition and round cell reaction (above). Newly formed capillaries (below). See also Figs. 123 and 124.

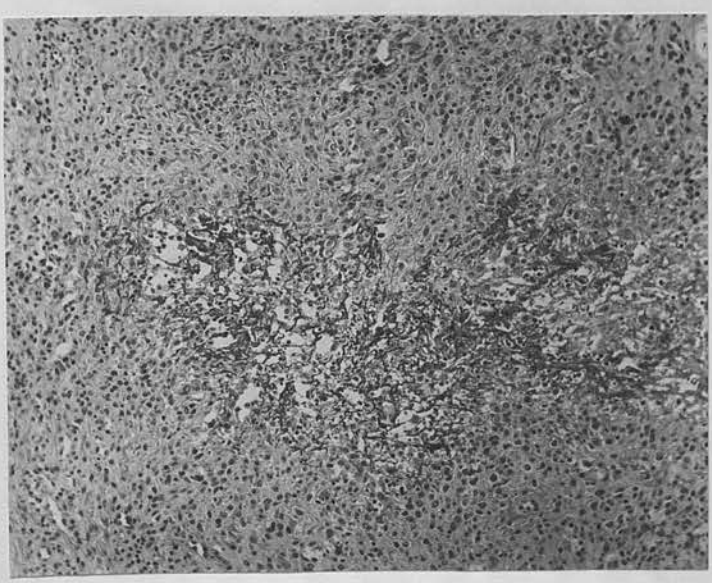

Fig. 123. Case 257 x 100. Nodule of six weeks' duration. Necrosis and fibrin deposition in a mass of proliferating mesenchymal cells. No intermediate layer.

Subcutaneous Nodule in Rheumatic Fever.

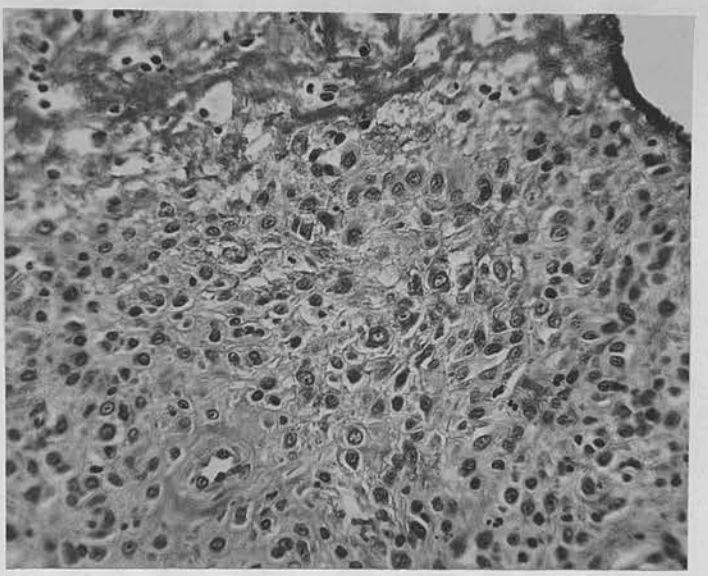

Fig. 124. Case 257 x 250. The edge of another necrotic focus in the nodule shown in Fig. 123. Note the fine fibres between the cells and the absence of an intermediate layer.

Subcutaneous Nodule in Polyarteritis Nodosa.

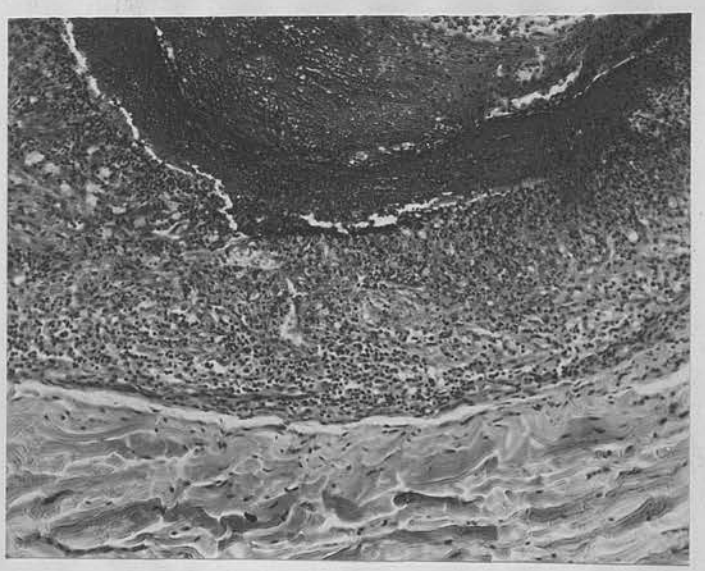

Fig. 125. Case 540 x 100. A thrombus (top) occupies the dilated lumen of a small artery, the whole wall of which is disorganised and acutely inflamed.

Nodules of Rheumatoid Type without Rheumatic Disease or Granuloma Annulare.

Four cases have been encountered in which lesions histologically indistinguishable from those of rheumatoid arthritis have been encountered in patients who had no history or evidence of rheumatic disease and who were not suffering from granuloma annulare.

a) A "lump" was removed from the elbow of a girl aged 4 (Case 938). The girl was otherwise completely healthy and has remained so ever a period of 18 mths. The nodule contained several small foci of rheumatoid type, but small and with the zonal arrangement incompletely developed. One larger focus was present showing early bursa formation in the central zone and a well-developed intermediate zone (Fig. 126). The outer zone was cellular and vascular fibrous tissue containing many diffusely distributed or perivascular round cells (Section sent by Dr. H.T.G. Strawbridge, Liverpool).

b) A small hard lump was removed from beneath the skin on the dorsum of the penis of a boy aged 4 (Case 939). No evidence of any rheumatic illness could be found nor were the clinical features suggestive of granuloma annulare. The nodule contained three foci, the smallest 500 x 260 μ, the largest of irregular L-shape and nearly 1 cm. in total length. The central zone of the largest contained/

Subcutaneous Nodule of Rheumatoid Type without Arthritis.

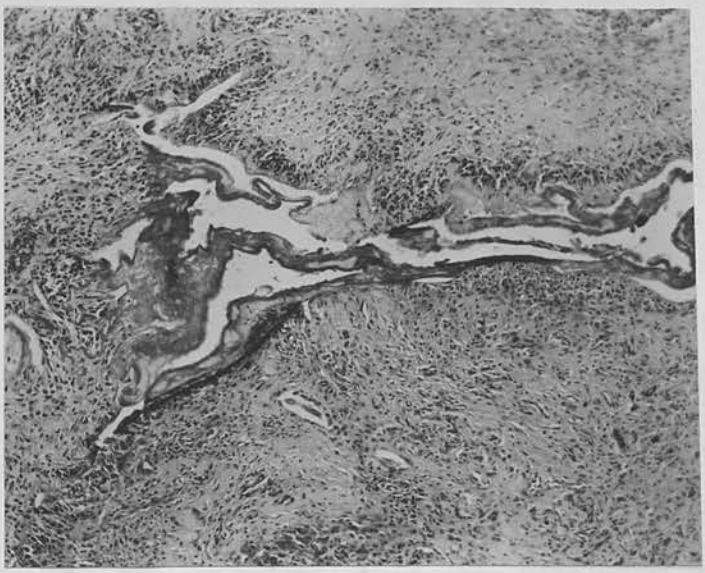

Fig. 126. Case 938 x 75.
Necrotic central zone is undergoing liquefaction to form an adventitious bursa lined by intermediate layer as in rheumatoid arthritis.
Compare with Fig. 100, p. 138.

contained a necrotic thrombosed capillary. The intermediate zone was well-developed and consisted mostly of large mesenchymal cells. It differed from the majority of rheumatoid nodules in containing a greater number of lymphocytes. The outer zone contained many newly-formed capillaries, moderate numbers of fibroblasts and a good many round cells both diffuse and perivascular in distribution (Fig. 127) (Section sent by Dr. D.H. Collins, Leeds).

c) A nodule of 4 mths. duration was removed from the back of the hand of a woman aged 20 who had a previous history of intercostal neuralgia and iritis but no involvement of joints (Case 936). The nodule had ulcerated so that many polymorphs were seen superficially. This did not obscure the zonal arrangement of the single focus present, which was approximately 2 mm. in diameter. The intermediate zone was incomplete but better developed than in granuloma annulare (Skin Department Case, SD 1105).

d) A woman aged 26 had juxta-articular nodules on the hands and feet for a year with no history or clinical features of rheumatic disease, syphilis or granuloma annulare (Case 937). The nodule contained one focus 1050 x 500 μ in diameter and 1100 μ from the surface and another incomplete focus cut by the line of excision. The central zone contained a little cellular debris/

Subcutaneous Nodule of Rheumatoid Type without Arthritis.

Fig. 127. Case 939 x 100. A necrotic thrombosed capillary is seen in the central zone (arrow). The intermediate zone is well developed and contains many lymphocytes. Compare with Fig. 78, p. 122 and Fig. 83, p. 127.

debris, the intermediate zone was complete and very cellular with fibroblasts predominant and only occasional lymphocytes. Vascular proliferation in the outer zone was quite marked and dense perivascular round cell infiltration was seen (Skin Department Case, SD 1171).

Non-rheumatic Nodules in Rheumatoid Arthritis and Rheumatic Fever.

Four nodules removed from cases of rheumatoid arthritis in the expectation that they would show the usual histopathological features had entirely different appearances :-

a) A nodule removed from a point on the right ulnar border distal to the usual site was found to contain metallic material. Histologically it consisted of a bursa-like cavity surrounded by dense hyaline fibrous tissue containing much haemosiderin. Further questioning of the patient revealed that he had sustained a shrapnel wound at this site in the 1914-1918 war (Case 106, Fig. 128).

b) A nodule of a year's duration removed from the dorso-lateral aspect of the left middle finger at the level of the distal interphalangeal joint proved to be a benign synovioma (giant-cell tumour of tendon sheath) (Case 109, Fig. 129).

c) A nodule was removed from the extensor aspect of elbow in the situation where rheumatoid nodules most commonly occur (Case 105). The

Non-rheumatoid Nodule in Rheumatoid Arthritis.

Fig. 128. Case 106 x 100. This nodule developed around a piece of shrapnel. It consists of hyaline fibrous tissue impregnated with iron salts (the darker zone). A few histiocytes are seen along the inner margin (top). The cells in the cavity are red cells introduced at biopsy.

Fig. 129. Case 109 x 100. This benign giant-cell synovioma has a characteristic appearance.

patient was a miner and the nodule had been present for some years prior to the onset of the arthritis. The clinical appearance was unusual in that there was a depressed scar over the nodule. On taking the biopsy material the nodule was found to be adherent to the periosteum to a much greater extent than usual. Histologically there was a superficial resemblance to the rheumatoid nodule in that strips of large cells in palisade arrangement were present. These cells were not related to necrotic foci, however, but lined cleft-like spaces which either contained blood or were empty (Fig. 130). Transitional stages could be seen between these vessels and others, which although newly formed and with swollen endothelium were more normal. The final distinction from a rheumatoid nodule and the diagnosis were indicated by the presence of refractile foreign material which had produced a focal granulomatous reaction (Fig. 131).

d) This patient presented the unusual combination of a histologically characteristic nodule on one elbow and a much larger nodule more distally situated on the other forearm. The latter was composed entirely of loose whorls of cellular fibrous tissue - it was a fibroma. It is interesting to speculate about the histological structure of nodules which were present on the left wrist and ankle (Case 98 : see Figs. 84 and 100).

Another/

Non-rheumatoid Nodule in Rheumatoid Arthritis.

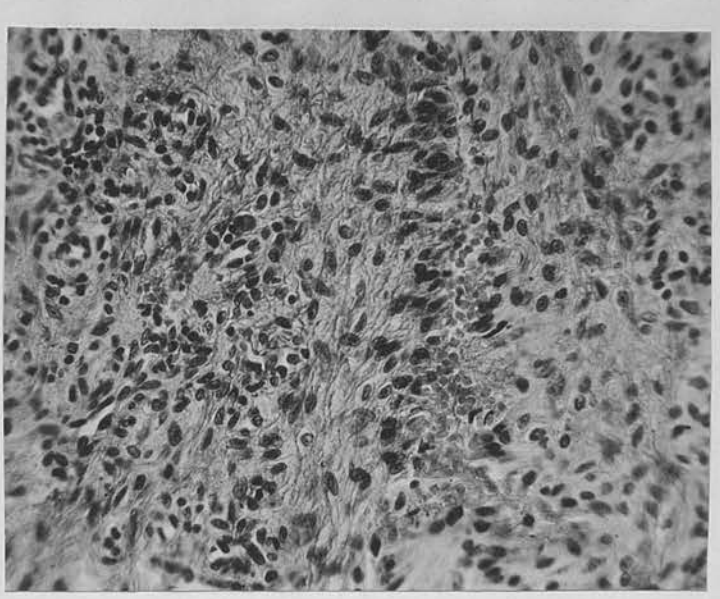

Fig. 130 Case 105 x 250. Palisade arrangement of cells along lumen of large capillary in a foreign-body granuloma. Cellular fibrous tissue around with many newly formed capillaries.

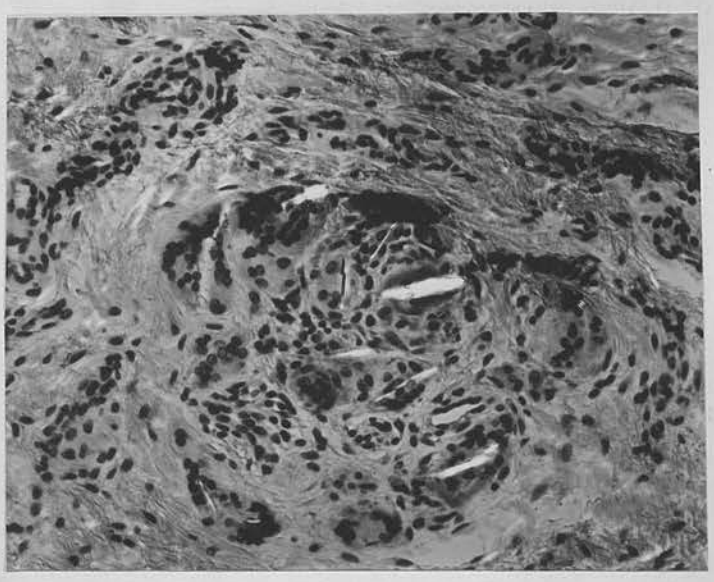

Fig. 131. Case 105 x 180. Photographed through partially crossed Nicol prisms. Another field from the same section as Fig. 130, showing a focal granulomatous reaction with giant cells around refractile cyrstals.

Another example of a subcutaneous lesion of non-rheumatoid type was obtained from a girl of 13 who had suffered from rheumatoid arthritis for 6 years (Case 108). For four years there had been small yellowish-white deposits 0·5 -1cm. in size over the interphalangeal joints of fingers on both hands. Clinically, these bore some resemblance to tophi, but the blood uric acid was only 4 mgm % and the clinical features did not suggest gout. Radiological examination revealed that the nodules contained calcium and a diagnosis of calcinosis circumscripta was made. This was confirmed histologically when the appearances were seen to differ considerably from those of the normal subcutaneous nodule, consisting instead of focal deposition of calcium salts with a non-specific granulomatous reaction including many foreign body giant cells (Fig. 132).

That subcutaneous lesions of non-rheumatic type occur in other rheumatic diseases was shown in a woman who had suffered from recurrent rheumatic fever over a period of 12 years (Case 262). Small nodules had been present over the metacarpophalangeal joints, elbows, knees, ankles and toes for 11 years and were definitely attached to the underlying tissues.

A nodule which was taken from the extensor tendon of the right middle finger consisted of tendon tissue with patchy fibroblastic activity. Necrosis/

Non-Rheumatoid Nodule in Rheumatoid Arthritis.

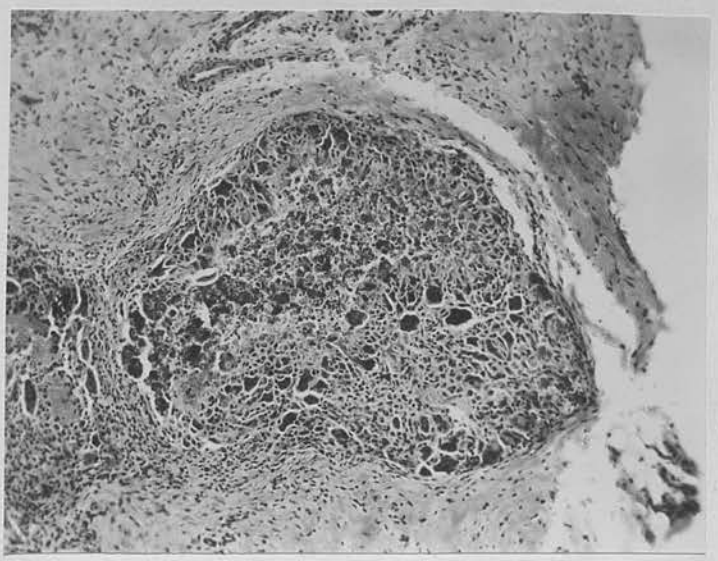

Fig. 132. Case 108 x 100. Granular deposits of calcium in calcinosis circumscripta with granulomatous reaction including many giant cells.

Necrosis was absent and inflammatory cells scanty. The significant feature was the presence of many cholesterol clefts along with large numbers of foamy histiocytes (Fig. 133). Unfortunately all the tissue was fixed in corrosive formol so no further identification of lipoid was possible. The appearances were quite different from the subcutaneous nodule of either rheumatic fever or rheumatoid arthritis being those of xanthoma.

Nodules in Non-rheumatic Diseases.

Nodular lesions from the elbow region in one case each of syphilis and yaws were examined :-

a) A woman of 64 with a + + WR who died of congestive cardiac failure was found at autopsy to have syphilitic aortitis and a gumma of the right main bronchus (Case 940). A large nodule had been present in the right elbow region for 6 months and had ulcerated. It consisted of large irregular areas of necrosis surrounded by vascular granulation tissue containing massive numbers of lymphocytes, plasma cells and histiocytes (Fig. 134). Occasional arterioles showed well marked endarteritis obliterans. The zonal arrangement of the rheumatoid nodule was lacking and the appearance was that of a gumma.

b) A juxta-articular nodule from a case of yaws (Case 941) consisted mostly of dense hyaline fibrous tissue containing scattered foci of necrosis (Fig. 135). A patchy reaction had occurred/

Non-Rheumatic Nodule in Rheumatic Fever.

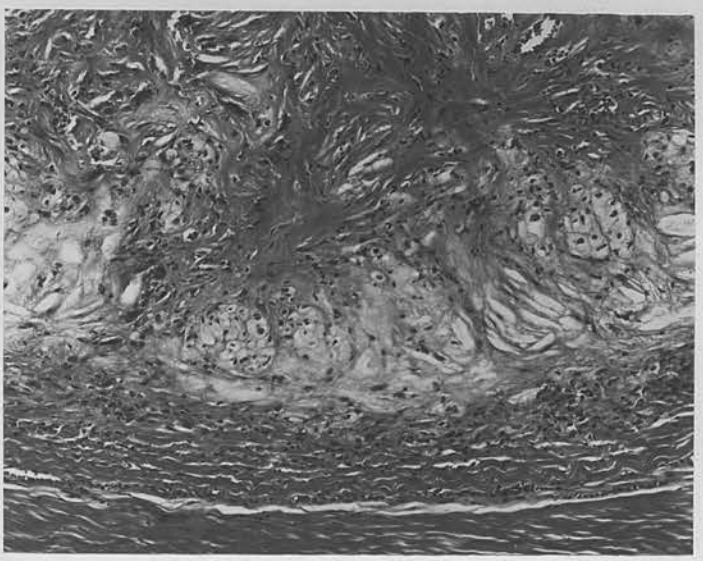

Fig. 133. Case 261 x 100. Many cholesterol clefts, foamy histiocytes, and proliferating fibroblasts are seen in the substance of this tendon, constituting a xanthoma.

Subcutaneous Gumma in Syphilis.

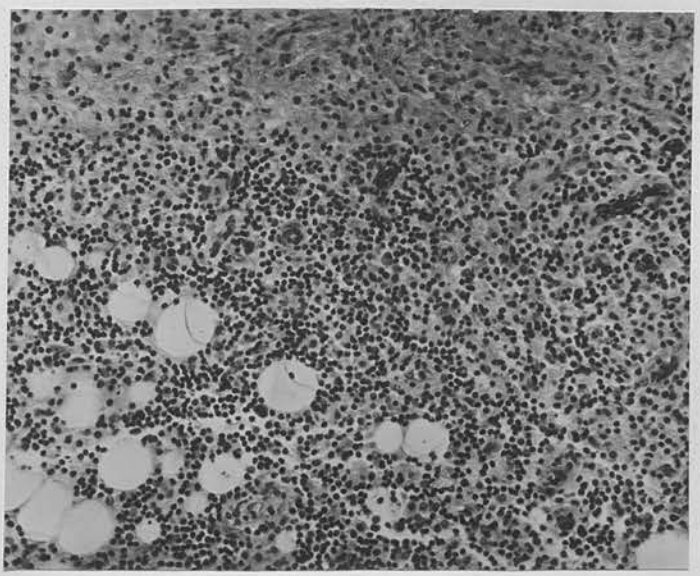

Fig. 134. Case 940 x 180. The central necrotic zone (above) merges gradually with the surrounding intense round cell infiltration. No intermediate layer is seen.

Subcutaneous Gumma in Yaws.

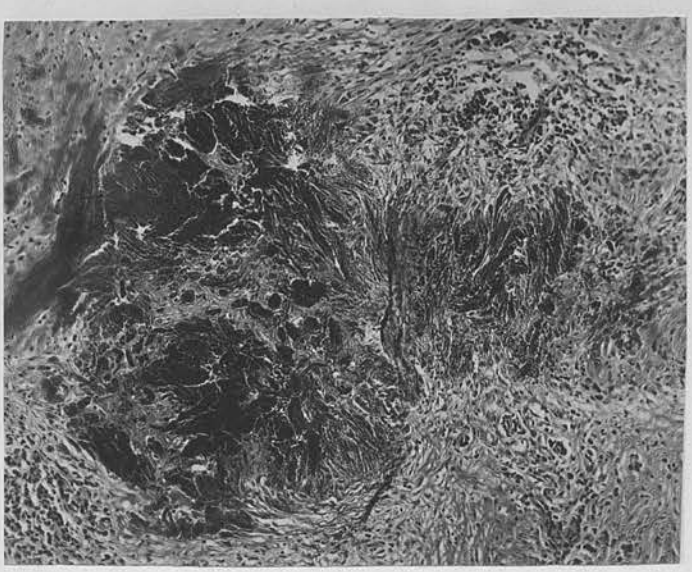

Fig. 135. Case 941 x 80. A necrotic patch lying in dense hyaline fibrous tissue has provoked focal plasma cell and lymphocyte infiltration.

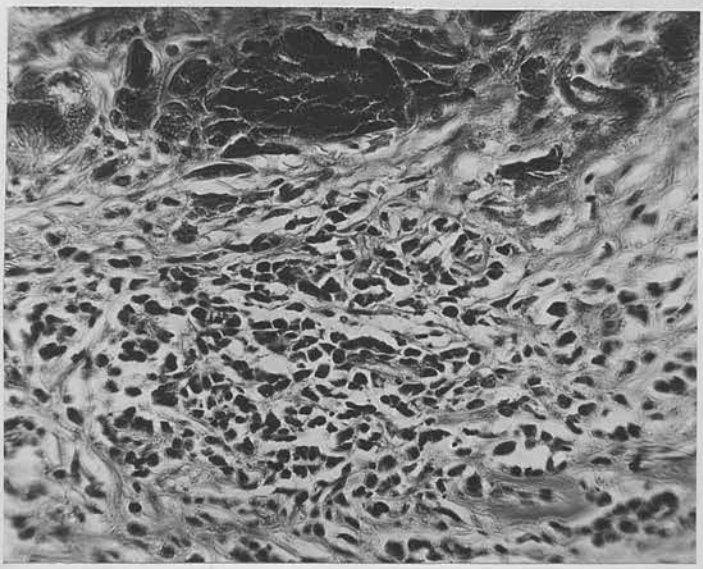

Fig. 136. Case 941 x 250. High power view of area in bottom left corner of Fig. 135.

occurred around these foci, in the form of foci of plasma cells and occasional lymphocytes or of polymorphs (Fig. 136). Occasional capillaries were also seen. Patches of fibroblastic proliferation were present and inflammatory cells of the types already mentioned were diffusely scattered through the tissue. A good deal of haemosiderin was also noted. No zonal arrangement was present and this lesion was interpreted as an old-standing, partially healed gumma.

Despite differences in anatomical distribution the lesions of rheumatoid arthritis resemble those of tuberculosis to some extent in their histological appearances. Thirty three of the 40 tuberculous lymph nodes examined, showed caseation and in 10 of these degenerating nuclei in the caseous areas were associated with diffuse basophilia such as was encountered in rheumatoid arthritis. Transition from healthy to karyolytic nuclei and basophilia of the granular material was seen and in these cases silver nitrate produced no reaction. Calcification was distinguishable by the presence of plaques of less granular basophilic material with a definite edge and in such instances a reaction was obtained with silver nitrate. Radial orientation of the epithelioid cells with palisading was seen only in one case. The appearances could be distinguished from rheumatoid nodule by the looser arrangement of the cells, the absence of collagen fibres, the thinner depth of the palisade/

palisade, the presence of many lymphocytes among the epithelioid cells and the presence of large Langhan's type of giant cells. The outer part of this zone was predominantly lymphocytic with varying numbers of fibroblasts. An outer fibrous zone, such as occurred in rheumatoid arthritis was not seen in the tuberculous nodes, whereas the latter frequently contained outlying small tubercles around the main caseous ones.

An interesting example of the differentiation of tuberculous lesions from rheumatoid nodules occurred in a case of rheumatoid arthritis in which extensive tuberculous lesions were present at death (Case 107). These comprised chronic bilateral fibrocaseous pulmonary tuberculosis, caseous tracheobronchial lymphadenitis and multiple tuberculomata of liver. Tubercle bacilli were present in large numbers in the sputum. The lesions in the liver and lymph nodes could be differentiated from subcutaneous nodules by the features noted above (Fig. 137).

No difficulty was experienced in distinguishing the 30 foreign body granulomata in non-rheumatoid patients from rheumatoid nodules. In most cases the foreign body responsible could be identified and the tissue reaction was either focal or diffuse granulation tissue with varying numbers of foreign body giant cells. No necrotic foci were seen and although vascular proliferation was frequent, the appearances noted in Case 105 were not seen.

All of the inclusion dermoid cysts were readily/

" Tuberculoma " of Liver.

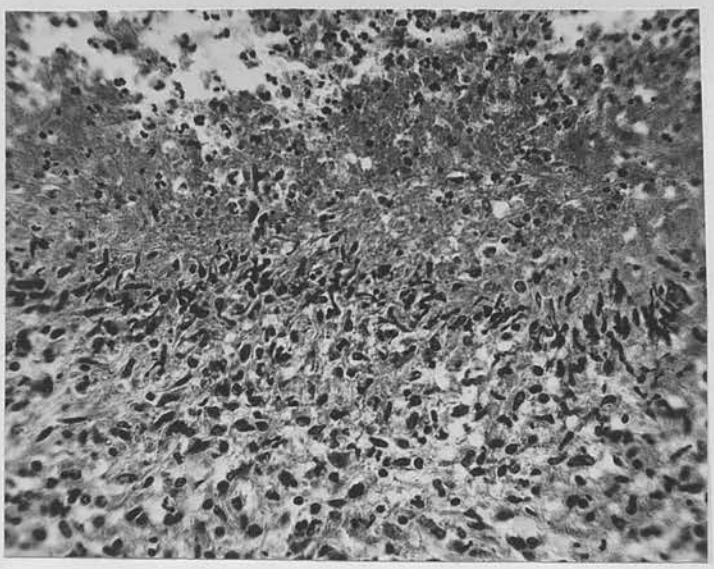

Fig. 137. Case 107 x 250. The caseous central zone contains nuclear debris and shows diffuse basophilia (Compare with Figs. 78 and 79, p. 122). It is surrounded by a broad layer of epithelioid cells and lymphocytes, the inner part of which is arranged radially. No collagen fibres are seen.

readily recognisable on account of the presence of squamous epithelium forming part at least of the lining. However, in one case the largest of two cysts present contained no epithelium and the cavity was lined by a narrow layer of round cells internal to which was an incomplete layer of large mesenchymal cells. This gave a slight resemblance to the appearances seen in some rheumatoid nodules, particularly the lipoid-containing ones, for the mesenchymal cells were histiocytes. The true nature of this cyst was revealed by its content of desquamated epithelial cells and keratin which was brightly refractile (Figs. 138 and 139).

The two traumatic nodules examined were both situated on the palmar aspect of the thumb, being on the right hand in one case and the left in the other. Both patients were men over 60 with clinical features suggestive of rheumatoid arthritis - pain, swelling and stiffness of the homologous hand and wrist in one and of both ankles in the other.

The nodules were very similar histologically, consisting of fibrofatty tissue with focal collections of round cells often near small vessels. The essential feature in both, however, was the presence of several small arteries showing old-standing recanalised thrombosis, with medial fibrosis and considerable loss of the internal elastic membrane (Fig. 140).

DISCUSSION/

Inclusion Dermoid Cyst.

Fig. 138. Case 1034 x 100. The cyst contains desquamated squamous epithelium and keratin and is lined by a layer of mesenchymal cells and histiocytes. Compare with Fig. 97, p. 135.

Fig. 139. Case 1034 x 100. The same field photographed by polarised light.
The refractile nature of the keratin is seen.

Traumatic Subcutaneous Nodule.

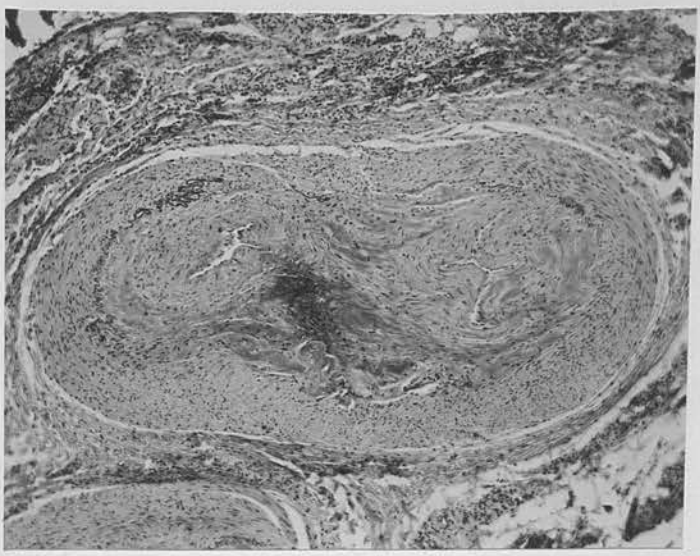

Fig. 140. Case 1036 x 50. A small artery shows old standing recanalised thrombus, partial loss of internal elastic lamina and medial fibrosis. Diffuse round cell infiltration in adjacent tissue. No evidence of arterial lesions elsewhere in body.

DISCUSSION.

Specificity of Nodules.

Comparison of the histopathology of the nodules of rheumatoid arthritis with that of lesions in granuloma annulare has shown that in the majority of cases the two conditions can be differentiated by a study of the tissue changes without reference to other features. The differences between the two are summarised in Table XXIV and were :-

a) Foci tended to become much larger in rheumatoid arthritis than in granuloma annulare.

b) In the central, necrotic zone, cellular debris and basophilic were much more pronounced in rheumatoid arthritis. Cholesterol deposition in this zone was also much more common in that condition.

c) The intermediate zone was usually better developed in rheumatoid arthritis, being not only more cellular but showing a greater tendency to radial arrangement and palisade formation. This was particularly true in foci of a size comparable with those seen in granuloma annulare. There was greater cellular activity / too, in the rheumatoid nodules, in the form of mitosis and multinucleate cells. Whereas large mesenchymal cells were markedly predominant in rheumatoid arthritis with few lymphocytes, this zone was usually more pleomorphic in granuloma annulare. As in the central/

Table XXIV.

Differences between Nodules of Rheumatoid Arthritis and Lesions of Granuloma Annulare.

Feature		Rheumatoid Nodule	Granuloma Annulare
Depth below surface *		Nearly all subcutaneous : cutaneous nodule 560 μ from surface	Nearly all cutaneous : <550 μ from surface in 5/10 cases. Deepest 900 μ
Central Zone	Size	Frequently 5 mm - 1 cm.	Usually 400-550 μ or less
	Cellular Debris	Frequent and marked	Inconspicuous
	Basophilia	In proportion to cellular debris	
	Cholesterol clefts	Present in 25%	Present in 1/10 cases
Intermediate Zone	Completeness	Frequent, especially in small foci	Incomplete
	Cellularity and Palisade	Many cells ; often marked palisade	Cells less numerous ; usually poor palisade
	Cytology	Mesenchymal cells, fibroblasts and histiocytes most numerous. Lymphocytes often present but in small numbers Giant cells in many cases	Mesenchymal cells etc. less numerous. Lymphocytes more numerous Giant cells not seen
	Mitosis	Commonly present	Unusual
	Capillaries	Present in 20% in outer part	Frequently present and throughout zone
	Cholesterol clefts	Present in 14%	Not seen
Outer Zone	Cellularity	Often marked	Usually slight
	Vascular proliferation	Frequent ; marked in 40%	Fairly frequent ; not marked.
	Perivascular infiltration	Frequent	Frequent
	Lesions of arterioles	Present in 45%; usually fibrosis ; occasionally inflammation	Infrequent ; slight fibrosis only.
Earliest lesion		Proliferation of mesenchymal cells	Degeneration of connective tissue

* Distance from surface of epidermis to nearest necrotic tissue.

central zone, cholesterol was more common in the arthritic nodules. There was greater vascularity in this zone in granuloma annulare, whereas capillaries were present in only one fifth of the rheumatoid nodules and were mostly in the outer part of this zone.

d) In the outer zone, cells of all kinds were more numerous and vascular proliferation was much more pronounced in rheumatoid arthritis. Vascular lesions were also more frequent in that condition and arteritis was confined to it.

e) Study of serial sections of the smallest lesions encountered suggested a difference in the initial change, namely that cellular proliferation was the first lesion in rheumatoid arthritis, followed by necrosis, whereas in granuloma annulare the cells occurred as a reaction to necrosis.

Some of these differences were noted by Bowers (1949) but the results obtained here differ in the degree of cellular disintegration seen in the two conditions. Furthermore, Bowers found vascular proliferation less marked in rheumatoid arthritis than in granuloma annulare. In that respect the present results agree rather with those of Goodman and Ketron (1936) mentioned above. The conclusions derived from the present study about the initial lesion can only be regarded as tentative in view of the small number of cases examined at that stage and/

and lack of experimental proof. Nevertheless they find support in previous studies (Kyrle, 1927; Goodman and Ketron).

Despite these differences, the lesions in the two conditions showed many points of similarity. In particular, occasional rheumatoid nodules contained some foci which resembled more closely those of granuloma annulare than those " typical " of rheumatoid arthritis. Most nodules of this type contained other foci which were more characteristically rheumatoid, but in one case the whole nodule resembled the lesion of granuloma annulare (Case 70, Fig. 83). Confusion of granuloma annulare with rheumatoid arthritis occurred only in Case 935, where the lesions were subcutaneous. However, in these two cases, as in others where histological examination was equivocal, appraisement of all features indicated the diagnosis. It should be noted especially that the subcutaneous lesions of granuloma annulare had been present for 6 years in Case 935. This is a much longer period of observation than the cases of Grauer (1934) and Tizard (1948) which were followed for " several weeks " and a year respectively. Although Klinge and Grzimek (1932) observed a patient in whom subcutaneous nodules preceded joint symptoms of rheumatoid arthritis by over two years, this is quite an exceptional mode of development of the disease. Failure to develop signs of rheumatic disease for 6 years after the onset, together with histological features/

features in keeping with those of the cutaneous lesions of granuloma annulare suggest that Case 935) is a true case of subcutaneous granuloma annulare and not a " forme fruste " of rheumatoid arthritis (Goodman and Ketron). No attempt has been made to use the newer histochemical techniques to differentiate rheumatoid nodules and granuloma annulare, for the writer agrees with Altschuler and Angevine (1949) that the present position with regard to the interpretation of degenerative changes in connective tissue is too confused to make such techniques of much value.

The occurrence in this study of patients free of rheumatic disease, but with nodules having a structure very similar to or identical with those of rheumatoid arthritis indicates that complete specificity cannot be attached to the changes which occur in that disease. Similar cases have already been quoted in the introduction to this section (See pp. 117-8). The question of prolonged follow-up is of great importance in such cases and it must be admitted that the longest period of observation of the present cases was eighteen months so that final judgement about all of them must be postponed.

That histological examination leads to an accurate diagnosis in most cases of rheumatoid nodules is indicated by the fact that the presence of the disease was unknown when the nodules from nine cases were examined (Cases 20, 61, 66, 82, 86/

86, 88, 96, 98 and 99). The histological diagnosis of a rheumatoid nodule was confirmed in each case by subsequent examination of the patient.

This series confirms the general opinion that nodules of rheumatoid arthritis are clearly distinguishable from those of gout or polyarteritis nodosa and these from one another. The rheumatic fever nodules could also be differentiated, although in Case 260, the intermediate zone was unusually well developed. The appearances in the two nodules removed at different times from Case 257 agree closely with the findings of Mote et alii (1937) in nodules of similar duration. The histological pattern in syphilis, yaws, tuberculosis nodules were quite different from those of rheumatoid and traumatic/arthritis and the other rheumatic diseases, though some of these nodules had a clinical resemblance to the arthritic ones and some of the patients complained of rheumatic pains. No support could be found for Bolgert's statement (1944) that rheumatoid nodules are identical with those of syphilis.

The occurrence in patients with rheumatic disease of six nodules having appearances quite different from those associated with the diseases in question serves as a reminder that such patients are as liable as others to acquire foreign-body granulomata, fibromata, xanthomata and giant-cell tumours. Because one of the foreign-body granulomata encountered in rheumatoid arthritis had a superficial resemblance/

resemblance in places to the rheumatoid nodule, a series of such lesions and of inclusion dermoid cysts was examined. All these lesions could be clearly identified when viewed as a whole, although in one dermoid part of the lesion had a superficial resemblance to the rheumatoid nodule (Case 1034, Figs. 138 and 139).

Histological Features of the Rheumatoid Nodule.

Observations, some of which are at variance with previous statements, have been made upon the histological features of the rheumatoid nodule. These concern the stages in the development of the nodule, the occurrence of calcification and of lipoid, the structure of nodules occurring in variants of rheumatoid arthritis and the occurrence of nodules in situations other than subcutaneous tissue.

It was possible to work out a histological cycle commencing with proliferation of mesenchymal cells (Fig. 94). This is in agreement with the opinion of Collins (1937) but disagrees with that of Kellgren and Ball (1950) who believed that nodules commence as a degeneration of collagen. It must be noted that both views are based on the use of chemically crude histological stains and that the primary stage may be in ground substance as suggested by Bywaters (1949) and Altschuler and Angevine (1949). Whatever the site and nature of the primary lesions, proliferation of mesenchymal cells/

cells preceded necrosis in this series. Failure of absorption or organisation of the necrotic material led to the formation of the three-zoned focus. Foci within a nodule frequently fused to form large, irregular necrotic masses in which cavitation or bursa formation sometimes occurred. Nodules of this structure persisted for years, increasing in size by formation of new foci or enlargement of old ones. Activity was often seen in nodules when the disease was inactive or apparently healed in other tissues. In the later stages some foci or the whole nodule underwent gradual hyaline transformation, but a more frequent change was deposition of lipoid and encapsulation as described by Collins (1937) and Fletcher (1951(b)). Rheumatoid nodules were rarely noticed by patients until they were of sufficient size to cause a considerable lump, so that it was not possible to obtain an accurate indication of the duration in most cases. This sequence of events, therefore, must be a purely histological concept, though it gains support from the presence of foci at several stages in many of the nodules.

Calcification was not seen radiologically or histologically in this series, many of the nodules being situated near joints which were X-rayed. Likewise no radiological evidence of calcification has been seen in many patients with nodules who have attended the Rheumatic Unit, Northern General Hospital/

Hospital or the Rheumatic Clinic, Royal Infirmary and in whom biopsy was not performed. Calcification of nodules was frequently mentioned in the literature prior to Keil's monograph (Wick, 1904 ; Freund, 1928-29; Findlay, 1931; Klinge and Grzimek, 1932; Weil and Delarue, 1932), and occasionally since then (See p. 111). However, few of these authors stated whether the calcium was recognised histologically or radiologically and none mentioned the use of silver nitrate in histological studies. The only convincing illustration of calcification is Fig. 23c of the article by Horwitz. It seems likely that much of the "calcification" mentioned in these papers was due to the basophilic material in the foci identified in the present study as nuclear debris rather than calcium by the Feulgen and Kóssa techniques. It should be noted that some previous workers failed to find calcium (Dawson, 1933 ; Collins, 1937, 1949 (f)) or found it very rarely (Rosenberg, 1949).

Cholesterol clefts were present in 11 subcutaneous or cutaneous nodules and were associated with foamy histiocytes in 6 of these. Foamy histiocytes were present without clefts in another 9 nodules, so that 20 out of the 51 nodules were shown to contain lipoid even without the use of fat stains. Recent papers on the presence of lipoid in these nodules have already been reviewed (p.111). It is sometimes overlooked that cholesterol was recognised in rheumatoid nodules/

nodules over twenty years ago (Crouzon and Bertrand, 1926 ; Freund, 1928-9 ; Dawson, 1933), and none of the recent authors referred to the work of Stewart (1916). Necrosis without means of escape for the products of disintegration was regarded by Stewart as one of the main causes of "cholesterin " deposition. Cholesterol clefts have also been described (Chauffard and Troisier, 1921 ; Chauffard and Wolf, 1923 ; Corneil and Paillas, 1936) and the substance isolated chemically from (Bunim and McEwen, 1940) tophi. It is interesting to note that the posterior tibial artery in one of the cases of arteriosclerosis included amongst the "non-rheumatic diseases" in Section IV had a decided resemblance to the cholesterol-containing nodules studied here (Case 1037, Fig. 141). Atheroma was one of the conditions excluded in Stewart's group of necrotic lesions.

The identity of the nodules from cases of "Felty's syndrome" and psoriatic arthritis with those from typical rheumatoid arthritis is in keeping with the opinion that these conditions are merely variants of the main disease. On the other hand, the nodule from juvenile rheumatoid arthritis appeared to lack the usual zonal arrangement. The piece of tissue examined from this patient was very small and serial sections were not available so that it must remain an open question whether this nodule was of rheumatoid or rheumatic type. The nodule removed from the patient who had been diagnosed as suffering from " palindromic rheumatism"/

Arteriosclerosis resembling Rheumatoid Nodule.

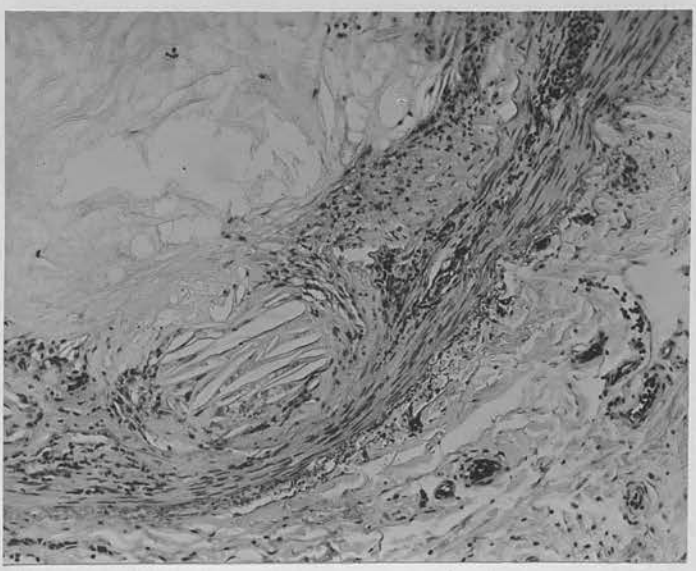

Fig. 141. Case 1037 x 100.
Cholesterol clefts in the thickened intima of a posterior tibial artery. Much atrophy of media. The arrow denotes the internal elastic lamina. Compare with Fig. 97, p. 135.

rheumatism" was of great interest because the clinical features at the time of biopsy suggested that rheumatoid arthritis proper was developing. Subsequent examinations of the patient proved that this was so and he has since responded well to gold therapy. The nodule removed appeared at first to be identical with that illustrated by Hench and Rosenberg (1949) in their Fig. 10, but more detailed examination revealed patches of necrosis, albeit of rather atypical appearance.

This study has confirmed previcus observations that nodules of rheumatoid arthritis are not confined to the subcutaneous tissue. Lesions found in the skin (Case 83), synovial tissue of the knee (Cases 33 and 201) and bursae (Cases 61 and 62) were identical with those found in the subcutaneous tissue. The lesions from the pharyngeal region of Case 1 and the heart of Case 2 had the same basic structure but differed in minor features mainly due to their situation, e.g., the "myocytes" seen in the cardiac lesions.

Serial Biopsies of Rheumatoid Nodules.

No serial biopsies of a single nodule were carried out, but analysis of the material available suggests that this procedure is of limited value in assessing the effects of treatment. Marked differences were noted in the appearances of nodules removed from different sites in the same patient as was done in Case 81 (back and knee) and

40 (metacarpophalangeal region and elbow). Furthermore, bilaterally symmetrical nodules of approximately the same age were studied in five cases and again showed marked differences. Thus, the appearances of nodules on the right and left elbows of Case 80 are shown in Figs. 94 and 103 : Fig. 102 shows the appearance of the nodule on the left below of Case 89, whereas that on the right side had a structure like that shown in Fig. 97. The presence even in a single nodule of several foci at different stages of development makes assessment of healing difficult, for there is no certainty that two blocks taken from it simultaneously would have identical appearances.

Studies such as those of Norcross et alii (1950) and Hunt and Blanchard (1951) in which the age and distribution of nodules removed before and after therapy were not stated must be accepted with reserve. On the other hand Fienberg and Colpoys (1951) and Mundy et alii (1951) studied scleral nodules which were all of the same crop so that the appearances before, during and after therapy were more comparable. Cortisone was used in both studies. Mundy et al saw no noteworthy change in histology after 18 days on local treatment and 13 days parenteral therapy (2.2 gm). Fienberg and Colpoys used only the parenteral route giving a total of 6.6 gm. cortisone in 39 days. In a series of biopsies they were able to trace disorganisation of the intermediate layer, liquefaction/

faction of the central zone and almost complete resolution in 31 days, followed by fresh necrosis a day after cessation of therapy. Their illustrations are convincing and suggest that they have described a real effect of the hormones since it is almost unknown for rheumatoid nodules to heal in so short a time.

SUMMARY.

1. The literature upon subcutaneous nodules in rheumatic diseases has been reviewed, paying particular attention to articles which have appeared since the monograph of Keil (1938). There is general agreement that the lesions occurring in rheumatoid arthritis, gout, rheumatic fever and polyarteritis nodosa are distinguishable from one another. Nodules of rheumatoid type occur in many tissues other than the usual site and they frequently contain lipoid. It has been claimed that treatment with cortisone and ACTH produce changes in the rheumatoid nodules. Although the histology of granuloma annulare is well known and it is frequently said to resemble the rheumatoid nodule, there are few detailed comparative studies of the two conditions. The literature on the occurrence of nodules of rheumatoid type in patients without stigmata of rheumatic is critically reviewed. Some of the cases reported are not acceptable but a few authentic cases/

cases are on record.

2. The object of this study was to determine the diagnostic value of histological examination of nodules in rheumatoid arthritis. Particular attention was paid to the difference between these nodules and the lesions of granuloma annulare.

3. The material studied included 51 subcutaneous and cutaneous nodules from 45 cases of rheumatoid arthritis and similar lesions in synovial tissue, bursae, the pharyngeal region and the heart; 10 biopsies from 9 cases of granuloma annulare, including two from a case with subcutaneous lesions ; tophi from two cases of gout ; 7 nodules from 5 cases of rheumatic fever ; nodules from two cases of polyarteritis nodosa. Four cases were included in which subcutaneous nodules of rheumatoid type occurred in the absence of any rheumatic stigmata or of granuloma annulare. Various non-rheumatic lesions studied included single nodules from cases of syphilis and yaws, 40 tuberculous lymph nodes and one tuberculoma of the liver, 33 foreign-body granulomata, 22 inclusion dermoid cysts, two traumatic nodules and two subcutaneous tumours.

4. The study indicated that rheumatoid nodules and granuloma annulare were distinguishable histologically in most cases, and the features differentiating/

differentiating the two were discussed. Consideration of clinical and other features completed differentiation in difficult cases. A long follow-up is necessary in suspected cases of subcutaneous granuloma annulare. It is suggested that the initial lesion in the rheumatoid nodule and in granuloma annulare is different.

5. The occurrence of nodules of rheumatoid type in the absence of that disease indicated that that lesion was not completely specific. Careful follow-up is again necessary in such cases, for nodules may precede joint symptoms in rheumatoid arthritis.

6. The subcutaneous lesions of gout and polyarteritis nodosa were quite distinctive : those of rheumatic fever were usually readily differentiated but showed features in common with the rheumatoid nodule.

7. Nodular lesions unconnected with rheumatic diseases were readily differentiated from the rheumatic lesions. Such nodules may occur independently in patients with rheumatic diseases and were seen on six occasions.

8. A histological cycle of events was observed in rheumatoid nodules. Calcification was not seen and reasons were given for doubting most of the previous reports. Cholesterol was frequently seen in rheumatoid nodules and is to be/

be expected because of the nature of the lesion. Nodules in " Felty's syndrome " and psoriatic arthritis were of the usual type. A nodule from a case of "palindromic rheumatism" was also of rheumatoid type though not quite typical.

9. The study of serial biopsies of nodules in attempts to assess reaction to treatment is likely to be of limited value. Reasons for this statement were discussed.

SECTION IV.

Focal Lesions in Skeletal Muscles in Rheumatic Diseases and Other Conditions.

INTRODUCTION.

A number of reports were published a few years ago describing the occurrence of focal collections of round cells in the skeletal muscles in rheumatoid arthritis (Steiner et alii, 1946 ; Clawson, 1946 ; Morrison, 1947 ; de Forest et alii, 1947; Gibson et alii, 1946 ; Desmarais et alii, 1948). Steiner et alii, who examined 14 cases and 196 controls claimed that the histological appearances in rheumatoid arthritis were specific. Some of the other workers found similar changes in other rheumatic diseases such as dermatomyositis, systemic lupus erythematosus and scleroderma (Morrison, et alii) and osteoarthritis (Desmarais et alii).

These reports led to the study of muscles from a large unselected series of cases by Clawson et alii (1947), who found round cell foci in 118 (26%) of 450 autopsies. The lesions were found in a wide variety of non-rheumatic diseases and in 25% of cases of accidental death in otherwise healthy persons. No attempt was made to distinguish different varieties of lesion.

Steiner and Chason (1948) maintained the view that the lesions found in rheumatoid arthritis were specific and could be differentiated from those seen in/

in other conditions, such as systemic lupus erythematosus, dermatomyositis and thromboangiitis obliterans. Sokoloff et alii (1950) also carried out a study in which different types of lesion were distinguished from one another, but concluded that the foci found in rheumatoid arthritis were not specific. Their 202 cases included 57 of rheumatoid arthritis, 89 of other rheumatic or arthritis diseases, 13 healthy volunteers and 43 miscellaneous conditions.

Very recently, Norcross et alii (1951) have carried out a study of biopsies of muscle from cases of rheumatoid arthritis before and after treatment with cortisone. Their results have so far been reported only in abstract form, but they claim to have seen " a definite alteration in the nodular infiltrates " in several of the 25 patients studied. A reduction in the " inflammatory changes" in skeletal muscle after ACTH has also been noted in one case of rheumatoid arthritis by Giansiracusa et alii (1951).

None of the workers cited above acknowledged that the presence of round cell foci in skeletal muscle has been recognised since the end of last century. The earliest report appears to be that of Askanazy (1898) who described collections of round cells in muscles of t he thorax, abdomen, pelvis, back, tongue and orbit in thyrotoxicosis. In 1905, Buzzard described focal collections of lymphocytes/

lymphocytes in quadriceps, rectus abdominis, orbital and other muscles in myasthenia gravis, and called them "lymphorrhages " by analogy with capillary haemorrhages. Mandelbaum and Celler (1908) were able to cite ten papers in which lymphorrhages were described. Geipel (1909) described round cell foci as distinct from Aschoff bodies in pectoralis, iliopsoas and thigh muscles in rheumatic fever. Dudgeon and Urquhart (1926) drew attention to the difficulty in finding lymphorrhages: in cases of thyrotoxicosis, they had to examine several muscles and many sections of each to find the lesions. Since then similar lesions have been described in Addison's disease (Duff and Bernstein, 1933), hypertension (Wagener and Keith, 1939 ; Foa et al, 1943), exophthalmic ophthalmoplegia (Brain, 1938), rheumatoid arthritis (Klinge and Grzimek, 1932 : Curtis and Pollard, 1940), dermatomyositis (Ogryzlo, 1948 ; Madden, 1950), gout, polyarteritis nodosa, subacute bacterial endocarditis, subacute combined degeneration, peripheral neuritis and fascioscapulohumeral muscular dystrophy (Ogryzlo, 1948) and systemic lupus erythematosus (Madden, 1950; Lowman, 1951 (a)). Meyenburg (1929) reviewed many papers on lymphorrhages and other lesions in muscles in general diseases.

No claim was made in any of these papers that the lesions were specific to any particular condition.

There/

There are conflicting opinions about the histology of muscles in dermatomyositis and scleroderma. Meyenburg (1929) emphasised that round cell infiltration in dermatomyositis was always diffuse whereas in scleroderma, lymphorrhages occurred. Freudenthal (1940) laid more emphasis on degeneration than on cellular infiltration and thought there was no essential difference between the two conditions. This view was shared by other British workers (Lewis, 1940 ; Dowling, 1940) and by some American workers (O'Leary and Waisman, 1943 ; Jager and Grossman, 1944). On the other hand Keil (1940) stated that the resemblances were only superficial. Brock (1934) stated that the two conditions resembled one another only in the early stages, being distinguishable later on.

In view of these conflicting opinions, it appeared desirable to study a large series of cases and to attempt to differentiate lesions in greater detail than has been done hitherto. The objects of this study are a) to determine whether a focal lesion specific to rheumatoid arthritis occurs in the skeletal muscles b) to attempt to determine the factor, or factors, responsible for the occurrence of lymphorrhages in skeletal muscles, and c) to ascertain the value of biopsy of a single piece of skeletal muscle in the diagnosis and of serial biopsies in the assessment of the effects of drugs in rheumatic diseases.

MATERIAL & METHOD

Blocks of skeletal muscle were obtained from 93 cases of rheumatoid arthritis. Twenty four cases were studied at autopsy, single blocks being taken from rectus abdominis, pectoral, diaphragm, psoas, deltoid, quadriceps and tongue in most cases and from various other muscles (gastrocnemius, popliteus, tibialis anterior, extensors of wrist, intercostal, pharynx) in some cases. The average number of blocks taken per case was seven. Material from the other 69 cases was obtained at biopsy the operation being performed by the writer. One or two blocks were taken from the extensors of the right wrist whenever possible. Occasional biopsies were taken from deltoid or quadriceps.

Blocks of muscle were obtained from 73 cases of " other rheumatic diseases ". Fifty three cases were studied at autopsy, blocks being taken as in the preceding group. The average number of blocks taken per case was four. Biopsies were obtained from the remaining 20 cases, 7 of these operations being conducted personally. Single blocks were obtained in most cases, but in some amputation specimens multiple blocks were obtained.

Specimens were also studied from 419 cases of non-rheumatic diseases. Two hundred and forty six of these cases were unselected routine autopsies from which multiple blocks were taken as in

rheumatoid/

rheumatoid arthritis. The average number of blocks studied per case was four. One or more blocks of skeletal muscle from 73 cases was available in the filed collections of the Pathology Department, Edinburgh University and Royal Infirmary. One or more blocks from the affected region from 47 cases in which muscle lesions were known to be present or were anticipated was available in the Neuropathology Department, Edinburgh Royal Infirmary. This group included diseases of the central nervous system, muscular dystrophies, prolonged ischaemia and denervation. In a further 53 cases, single blocks were taken during surgical operations.

The biopsies performed by the writer were mostly carried out at the Rheumatic Unit, Northern General Hospital. They were done under local anaesthesia with 2% procaine, care being taken to avoid infiltrating the specimen with local anaesthetic. In most cases, the anaesthetic infiltrated the skin and subcutaneous tissue only, for the removal of small pieces of non-anaesthetised muscle caused little or no inconvenience to the patient. The only special instrument used was an Allport's self-retaining retractor. This was used to retract skin and subcutaneous tissue and it helped to stop bleeding as well as providing an adequate field of operation. No attempt was made to suture the muscle after removal of the blocks. The small skin incision was closed with maltress sutures and

a/

a firm bandage used to prevent any oozing. No post-operative complications occurred in the 76 muscle biopsies performed. The pieces of muscle, which measured approximately 1.5 x 0.7 x 0.3 cm. were wrapped in gauze moistened with saline and fixative (usually corrosive formol) added after two hours. The study of blocks of muscle fixed at varying intervals after four amputations showed that by delaying fixation until two hours after removal from the body the distortion and shrinkage due to contractility was reduced to a minimum.

Blocks from both biopsies and autopsies were embedded in paraffin, single sections being cut and stained with haematoxylin and eosin. Serial sections were obtained and extra stains, such as Masson's trichrome, Weigert's elastin, van Gieson's and Giemsa's stains used when necessary.

RESULTS.

The incidence of all focal lesions other than degeneration confined to muscle fibres is shown in Table XXV. These lesions can be divided into two groups. The first contains the single focus which appeared to be the same as the " lymphorrhage " of Buzzard and will be designated by that term. This was by far the commonest lesion seen. The second group contains all foci which differed qualitatively from the lymphorrhage : these have been termed collectively " other focal lesions. " Many cases showed/

Table XXV.

Incidences of all Focal Lesions in Skeletal Muscles.

	Total Cases	Positive Cases	
		No.	Per cent
Rheumatoid Arthritis	* 93	42	45
Other Rheumatic Diseases	73	32	44
Non-rheumatic Diseases	419	57	14
Total	585	131	22

* Includes 11 cases with previous history, clinical or pathological features of rheumatic heart disease (5 positive).

showed only either lymphorrhages or other focal lesions, but in some cases both types were seen. In such cases, some muscles contained only one type of focus whereas in others several different lesions were seen. As one of the objects of the investigation was to determine the diagnostic value of a single piece of muscle, the cases have been analysed separately in respect of the two groups of lesions.

Lymphorrhages.

A lymphorrhage was most frequent endomysial, between muscle fibres (Figs. 142 and 143) or perimysial, in the connective tissue septa between muscle bundles (Figs. 144 and 145). Some of the larger foci were both endomysial and perimysial (Fig. 146). Occasional foci were epimysial, in the connective tissue on the surface of the muscle (Fig. 147-8)(See Table XL). The perimysial and epimysial foci were frequently related to arterioles and venules, sometimes as a cuff more or less completely surrounding the vessel, infiltrating only the adventitial coat (Fig. 149) and sometimes merely lying close alongside such a vessel (Figs. 144, 148, 150 and 151). Involvement of the media or intima of a vessel was interpreted as arteritis or phlebitis, and foci showing such lesions were classified among the other focal lesions. Apart from inflammation, the walls of perimysial arteries and arterioles sometimes showed excess of plain muscle/

Skeletal Muscle in Rheumatoid Arthritis.

Fig. 142. Case 120 x 70. Extensor of wrist. Three lymphorrhages, two fairly large endomysial and one perimysial.

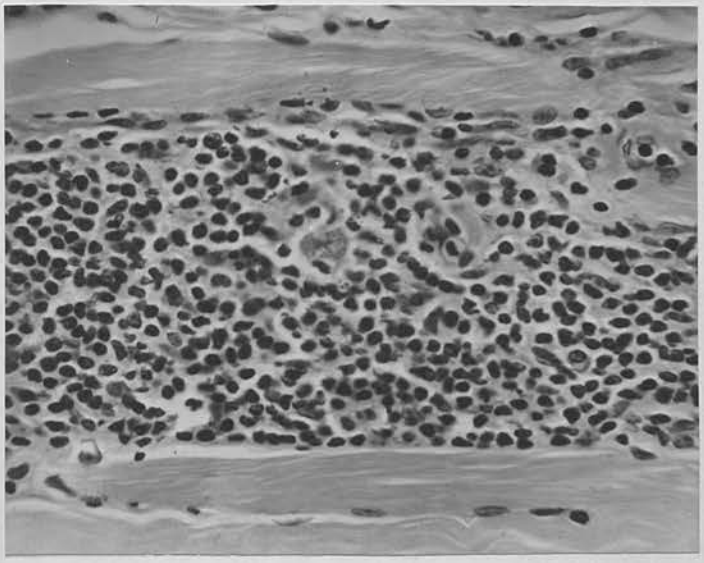

Fig. 143. Case 120 x 425. Part of focus in lower half of Fig. 142. The cells are mostly lymphocytes, with a few histiocytes and plasma cells. Subsarcolemmal nuclei and a capillary are seen at the upper margin of the focus.

Skeletal Muscle in Parkinsonism.

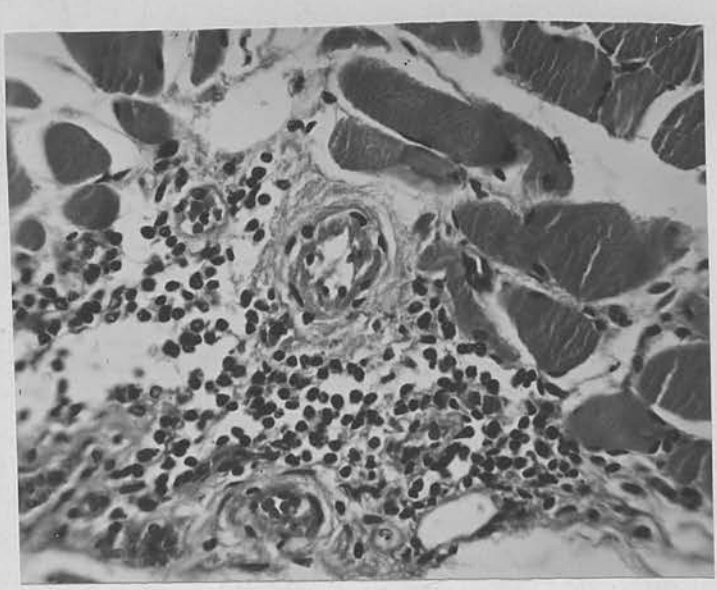

Fig. 144. Case 1111. x 375. Pectoralis major. Small perimysial lymphorrhage consisting almost entirely of lymphocytes. Two arterioles show intimal fibrosis.

Skeletal Muscle in Anencephalic Foetus.

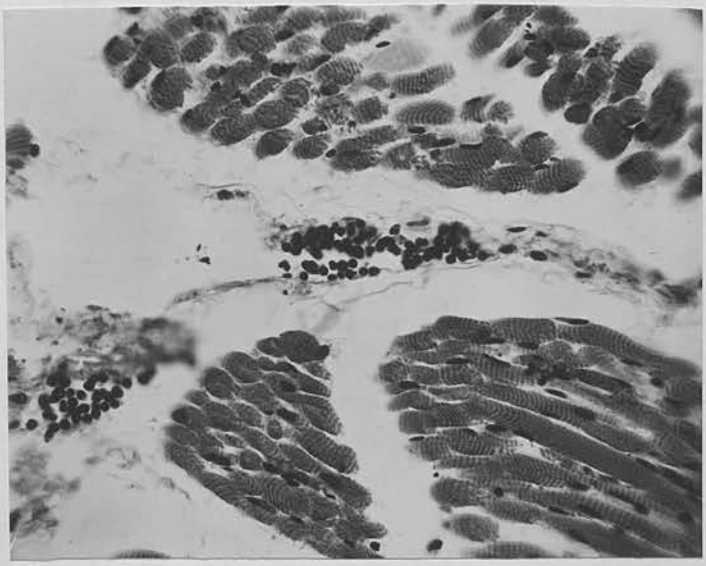

Fig. 145. Case 1158. x 300. Pectoralis major. Two small perimysial lymphorrhages. Several others were present in the section.

Skeletal Muscle in Scleroderma.

Fig. 146. Case 537 x 80. Two lymphorrhages of both endomysial and perimysial location. Moderate atrophy of muscle fibres is also present. See also Fig. 168, p. 241. The patient also had hypertension and cystic disease of the lungs.

Skeletal Muscle in Rheumatoid Arthritis.

Fig. 147. Case 170 x 80. Diaphragm. Small lymphorrhages in epimysial connective tissue (above centre) with loose infiltration (right centre). See also Fig. 161, p. 236. The patient also had pulmonary tuberculosis.

Skeletal Muscle in Rheumatoid Arthritis.

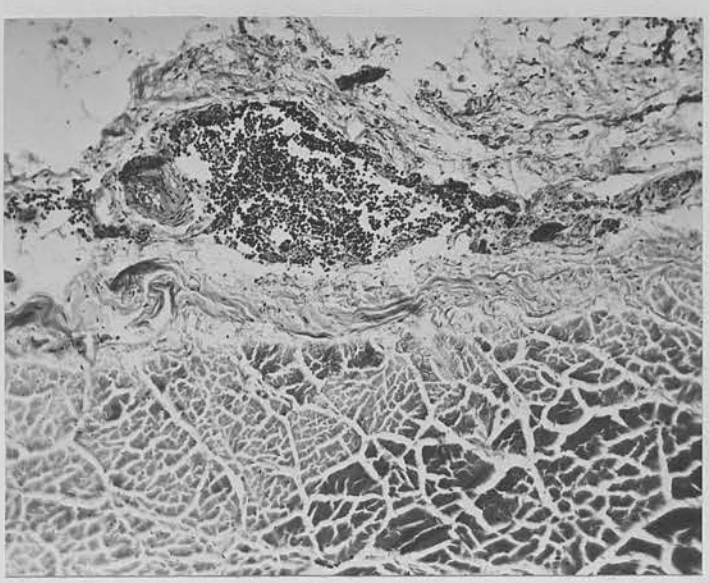

Fig. 148. Case 13 x 85. Pectoralis major. Lymphorrhages in connective tissue adjacent to a tendon. Note thickening of walls of arterioles. See also Fig. 153, p. 208 ; Fig. 156, p. 234 ; Fig. 169, p. 242.

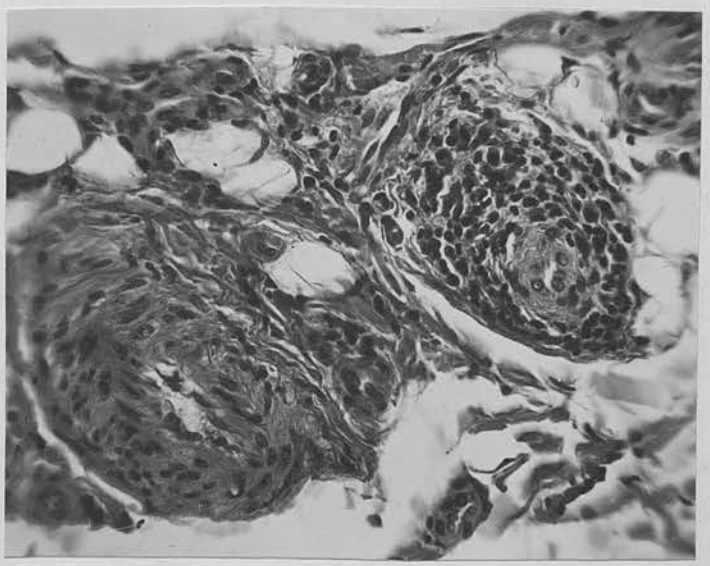

Fig. 149. Case 62 x 250. Extensor of wrist, in vicinity of bursa. Lymphorrhage surrounding an arteriole. Both this and the adjacent artery have thickened walls. The patient also had bronchiectasis and calcinosis circumscripta.

Skeletal Muscle in Rheumatoid Arthritis.

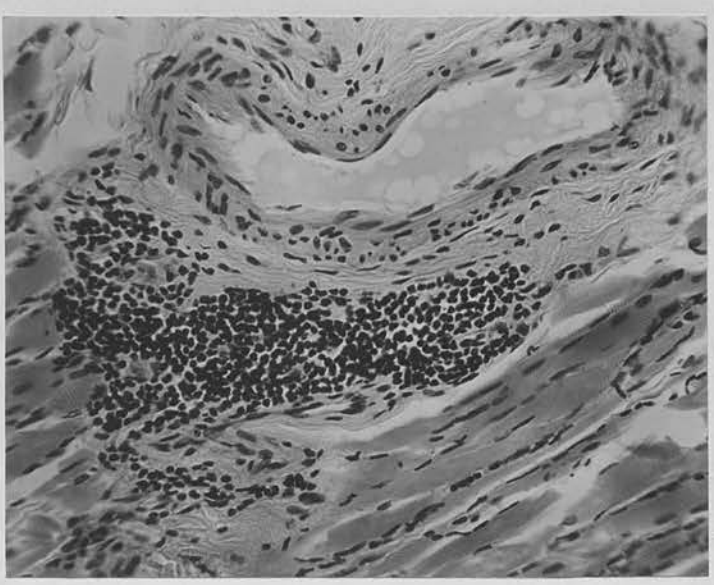

Fig. 150. Case 9 x 250. Extensor of wrist. Perimysial lymphorrhage lying alongside a small artery without involving its walls. Muscle fibres are atrophic. The patient also had pulmonary tuberculosis.

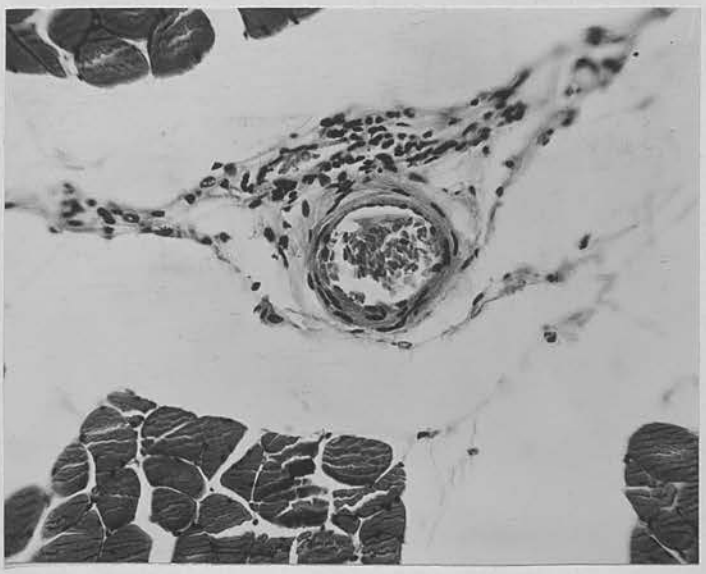

Fig. 151. Case 10 x 250. Rectus abdominis. This perimysial focus of just over fifty cells represents the minimal size of a lymphorrhage. The patient also had uraemia following chronic pyelonephritis and renal amyloidosis.

muscle in the intima, or intimal fibrosis even in patients who were not hypertensive (Figs. 144 and 149). Large foci in all three situations contained numbers of capillaries and these were usually the only vessels in endomysial foci (Fig. 152). Occasionally, perimysial foci involved the connective tissue surrounding small nerve bundles. No lymphorrhages or other foci were seen in muscle spindles.

The lymphorrhages varied considerably in size and shape. The largest were clearly visible on naked-eye examination of the stained sections, measuring up to 2 mm. in their long axis (Fig. 153). The smallest infiltrations accepted as foci consisted of 50 cells grouped in nodular fashion (Fig. 151). The shape depended to some extent on site, for endomysial foci were probably forced by the pressure of adjacent muscle fibres to become elongated or spindle-shaped (Fig. 142), whereas perimysial or epimysial foci assumed various shapes (Figs. 144,145, 146 and 150). In all sites, slender processes of cells commonly extended for a short distance from the main focus. Because of this variation in outline, measurement of the size of foci was difficult and sometimes impossible. For purposes of comparison, however, the largest focus in each section was measured in two diameters at right angles to one another. All the sections were cut at the same thickness, so the products of these diameters gave a rough indication of the size of the foci./

Skeletal Muscle in Rheumatoid Arthritis.

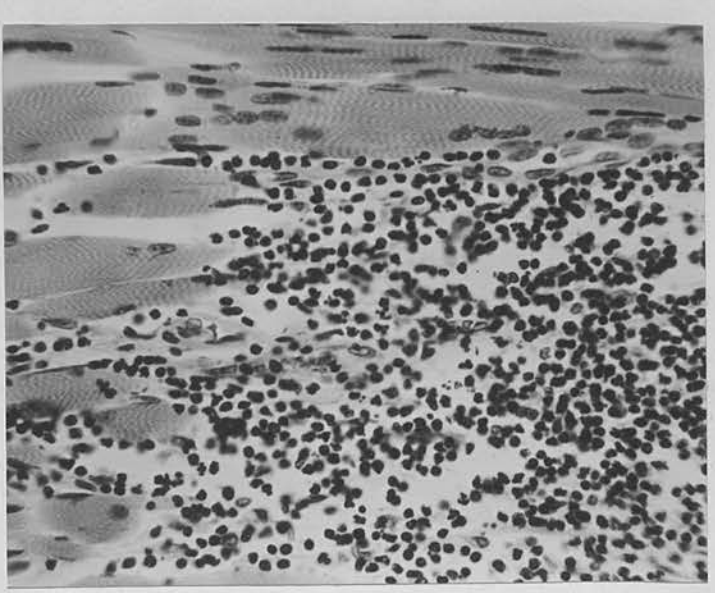

Fig. 152. Case 2 x 375. Quadriceps. Large endomysial lymphorrhage showing pyknosis and karyhorrhexis. Some muscle fibres are atrophic. See also Fig. 154, p. 210.

Fig. 153. Case 13 x 70. Rectus abdominis. The largest lymphorrhage encountered in skeletal muscle. Some muscle fibres are atrophic.

foci.

Lymphorrhages of all sizes had the same histological features. They consisted of closely packed cells, the distance between individual cells being usually less than twice the diameter of an average cell. The majority of the cells were lymphocytes and in many foci these were the only cells seen (Figs. 143-145, 149-152, 154). Plasma cells were present in many of the foci and were best seen peripherally, although they occurred in small numbers throughout these foci (Figs. 149, 155). Large cells of histiocytic or endothelial type were often scattered in small numbers through the foci (Fig. 143). Serial sectioning showed that cells of endothelial type, apparently lying in solid clumps, were really capillary endothelium (Figs. 143, 150, 152, 154). Polymorphs, eosinophils and fibroblasts were absent or present only in small numbers. Red blood cells were not seen. In some of the largest foci, there was a central area which a superficial resemblance to the germinal centre of lymphoid follicles. Closer inspection, showed that such foci consisted of pyknotic and karyhorrectic lymphocytes and small numbers of histiocytes arranged more loosely than elsewhere in the foci (Fig. 152). Apart from this central patch of degeneration, which was only occasionally seen, there was no tendency towards grouping of the cells in zones or areas. In some foci,

degenerating/

Skeletal Muscle in Rheumatoid Arthritis.

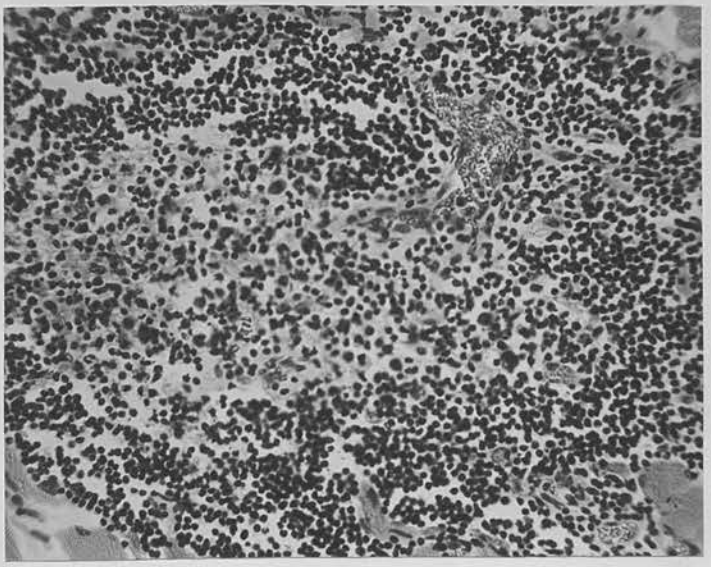

Fig. 154. Case 2 x 230. Quadriceps. Large endomysial focus with apparent germinal centre of loosely arranged lymphocytes and histiocytes.

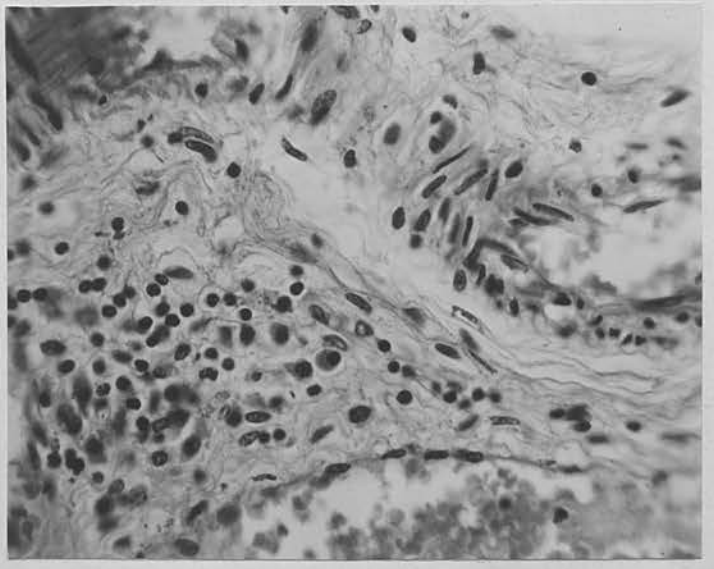

Fig. 155. Case 1 x 425. Pectoralis major. Plasma cells at periphery of perimysial lymphorrhage.

degenerating lymphocytes were scattered irregularly among the healthy cells.

The lymphorrhages were not encapsulated and contained no definite connective tissue framework, although small quantities of the connective tissue of the muscle itself might be seen. Degeneration of collagen was not seen in lymphorrhages : its presence was one reason for classifying a focus among the other focal lesions. Presence of fibrin and blood pigment were other reasons for regarding foci as atypical.

The incidences of lymphorrhages in rheumatoid arthritis, other rheumatic diseases and non-rheumatic diseases is shown in Table XXVI. The difference between the incidences in non-rheumatic diseases and rheumatoid arthritis is significant (P is less than .01). The difference between the incidences in non-rheumatic diseases and other rheumatic diseases is also significant (P is less than .01). The difference between the incidences in rheumatoid arthritis and the other rheumatic diseases is not significant (P is less than .20). The incidences of lymphorrhages in the muscles studied most frequently is shown in Table XXVII.

Factors Responsible for the Occurrence of Lymphorrhages in Skeletal Muscles.

Amongst 53 cases of rheumatoid arthritis in which no evidence of any other disease was found, the incidence of lymphorrhages was 41% (22 cases) whereas/

Table XXVI.

Incidences of Lymphorrhages in Skeletal Muscles.

	Total Cases	Positive Cases	
		No.	Per cent
Rheumatoid Arthritis	* 93	39	42
Other Rheumatic Diseases	73	24	33
Non-rheumatic Diseases	419	35	8
Total	585	98	17

* Includes the same cases as in Table XXV (5 positive).

Table XXVII.

Incidence of Lymphorrhages in Certain Muscles.

	Rheumatoid arthritis			Other rheumatic diseases			Non-rheumatic diseases		
	Total blocks	Positive blocks		Total blocks	Positive blocks		Total blocks	Positive Blocks	
		No.	%		No.	%		No.	%
abdominis	19	5	26	26	5	19	222	6	3
lis	19	9	47	29	3	10	195	4	2
gm	19	7	44	29	7	24	192	15	8
	17	4	23	18	4	22	80	4	5
eps	34	11	32	25	8	32	83	3	4
	26	7	27	13	3	23	23	1	4
r of wrist	101	28	28	7	2	29	13	1	8
	23	1	4	7	1	14	29	1	3
emius	2	0	0	12	2	17	57	4	7

whereas among 40 cases in which various other pathological processes were present it was 50% (20 cases). Although the difference is not significant it appeared possible that the presence of lesions in addition to those of rheumatoid arthritis was influencing the incidence.

Accordingly those cases of rheumatoid arthritis, in which there was no evidence of any other disease, were analysed to see whether any correlation could be found between such factors as age, duration, activity or stage of the disease, or the source of the muscle examined in relation to the proximity of lesions in other tissues and the incidence of foci. The age-incidences are seen in Table XXVIII - the figures here are too small for statistical analysis, but the high incidence in the fourth decade is interesting for there is a similar distribution in non-rheumatic diseases (Table XXXV)/. (p.223). The relationship between presence of lymphorrhages and the duration in 50 cases is seen in Table XXIX. Here again the figures are too small for statistical analysis, but there is a suggestion that foci are more likely to be found in cases of over a year's duration then in cases of shorter duration. The difference in the incidences of foci in active and inactive cases is shown in Table XXX. The amount of damage sustained by the joints or the stage of the disease (Steinbrocker et al., 1949) is perhaps a more accurate measure of its progress than either the/

Table XXVIII

Age-incidences of Lymphorrhages in Skeletal Muscles in Rheumatoid Arthritis.

Age	Total Cases	Positive Cases	
		No.	Per cent
20 - 29	9	3	33
30 - 39	7	5	72
40 - 49	11	3	27
50 - 59	16	4	25
60 - 69	8	5	62
70 - 79	2	1	50
Total	53	21	40

Table XXIX

Relationship between Duration of the Disease and the Incidence of Lymphorrhages in Skeletal Muscles in Rheumatoid Arthritis.

Duration	Total Cases	Positive Cases	
		No.	Per cent
Less than 1 year	13	3	23
1 - 4 year	18	9	50
More than 4 years	19	9	47
Total	50	21	42

Table XXX

Relationship between Activity of the Disease and the Incidence of Lymphorrhages in Skeletal Muscles in Rheumatoid Arthritis.

	Total Cases	Positive Cases	
		No.	Per cent
Active Rheumatoid Arthritis	45	18	40
Quiescent or Inactive Rheumatoid Arthritis	5	3	60
Total	50	21	42

the duration or activity. The incidences of lymphorrhages at various stages of the diseases is shown in Table XXXI. No significant differences are obtained. Most of the blocks of muscle studied were taken from sites which were not near affected joints, some were taken from a muscle as near to an affected joint as practicable and a few were in contact with subcutaneous nodules or synovial tissue of active joints. In Table XXXII are recorded the findings in those cases where information about the activity in individual joints was available.

The incidences of lymphorrhages in the individual disease in the " other rheumatic diseases " is seen in Table XXXIII and the age incidences in the whole group in Table XXXIV. In both tables the numbers are too small to be analysed statistically.

The cases of non-rheumatic disease were analysed to see whether age or any particular disease or group of diseases was associated with a significantly high incidence of lymphorrhages. The age-incidences are seen in Table XXXV where it will be noted that the highest incidence was in the fourth decade as in rheumatoid arthritis (See Table XXVIII) (p.215). Many cases in this group had two or more distinct diseases present. A list of the individual diseases which, singly or in different combinations, were associated with lymphorrhages is contained in Table XXXVI. The influence/

Table XXXI.

Relationship between the Stage of the Disease and the Incidence of Lymphorrhages in Skeletal Muscles in Rheumatoid Arthritis.

Stage	Total Cases	Positive Cases	
		No.	Per cent
a) Cases in which no disease process other than rheumatoid arthritis was present.			
I	17	6	35
II	15	6	40
III	4	1	25
IV	7	5	71
Total	43	18	42
b) All cases of rheumatoid arthritis, including those in a)			
I	17	6	35
II	18	9	50
III	14	8	57
IV	14	10	71
Total	63	33	52

Table XXXII

Relationship between the Source of the Muscle and the Incidence of Lymphorrhages in Skeletal Muscles in Rheumatoid Arthritis.

Source of muscle	Total Blocks	Positive Blocks	
		No.	Per cent.
Unrelated to a nodule or affected joint	47	12	26
Near an active joint	45	12	27
In contact with a nodule or affected joint	9*	3	33
Total	91	27	30

* This group includes 7 cases in which lesions other than rheumatoid arthritis were present : two of these cases were positive.

Table XXXIII.

Incidences of Lymphorrhages in Skeletal Muscles in Other Rheumatic Diseases.

Diagnosis	Total Cases	Positive Cases	
		No.	Per cent
Ankylosing spondylitis	6	1	17
Osteoarthritis	9	3	33
Gout	1	0	0
*Rheumatic fever	32	7	22
Systemic lupus erythematosus	5	4	80
•Polyarteritis nodosa	8	2	25
†Dermatomyositis	7	3	43
°Scleroderma	5	4	80
Total	73	24	33

Key :

* = includes subacute bacterial endocarditis (4 cases, 2 positive).
• = includes one case with rheumatic heart disease as well (negative).
† = includes one case with polyarteritis as well (negative).
° = includes one case with mitral fibrosis (positive).

Table XXXIV

Age-incidences of Lymphorrhages in Skeletal Muscles in Other Rheumatic Diseases.

Age	Total Cases	Positive Cases	
		No.	Per cent
1 - 9	1	0	0
10 - 19	9	4	44
20 - 29	13	5	38
30 - 39	9	3	33
40 - 49	16	5	31
50 - 59	8	3	37
60 - 69	11	2	18
70 - 79	4	2	50
Total	71	24	34

Table XXXV.

Age-incidences of Lymphorrhages in Skeletal Muscles in Non-rheumatic Diseases.

Age	Total Cases	Positive Cases	
		No.	Per cent
Foetus	5	0	0
Stillbirth & Neonatal	23	1	4
1 - 9	5	0	0
10 - 19	14	1	7
20 - 29	32	3	9
30 - 39	48	7	15
40 - 49	60	5	8
50 - 59	78	6	8
60 - 69	82	6	7
70 - 79	44	2	4
80 - 89	11	1	9
Total	402	32	8

Table XXXVI.

Alphabetical List of Diseases in Which Lymphorrhages were found in Skeletal Muscles.

Agranulocytosis
? Allergic lesions in spleen and lymph nodes
Amyloidosis
Anencephalus
Ankylosing spondylitis
Anthraco-silicosis
Appendicitis
Atheroma of cerebral arteries
Atheroma of coronary arteries

Bronchitis, bronchiectasis

Carcinoma, primary site in breast, bronchus, cervix uteri, colon, kidney, ovary, pancreas, prostate, stomach, thyroid
Cholecystitis
Cholelithiasis
Cirrhosis of liver
Cystic disease of lungs

Dermatomyositis
Diabetes mellitus
Disseminated lupus erythematosus
Disseminated sclerosis
Duodenal ulcer

Emphysema
Encephalitis, viral

Friedreich's ataxia

Gastric ulcer
Glomerulonephritis, acute
Gold, toxic reaction to

Hepatitis, viral

Immersion foot
Infarcts, thalamic

Myasthenia gravis, with and without thymoma
Myocarditis, acute and subacute non-specific
Myxoedema

Nephrosclerosis, benign
Nephrosclerosis, malignant with death from cardiac failure or uraemia

Osteoarthritis

Parkinsonism
Pneumonia, bronchopneumonia
Pneumonia, streptoccal
Poliomyelitis
Polyarteritis nodosa
Polyneuritis/

Polyneuritis
Pregnancy
Psoriasis
Pyelonephritis, pyelitis, cystitis

Rheumatic fever, acute and healed
Rheumatoid arthritis

Scleroderma
Senile hyperplasia of prostate
Septicaemia, meningococcal
Septicaemia, streptococcal
Subacute bacterial endocarditis
Thromboangiitis obliterans
Thrombocytopoenic purpura
Trauma, fractured femur with death within a week
fractured skull with transverse myelitis
Tuberculosis, primary in lung
chronic pulmonary, with tuberculous bronchopneumonia, ileitis and colitis
chronic pulmonary with healed tuberculosis of suprarenals and Addisons's disease
acute miliary
pulmonary with early miliary

Volkmann's ischaemic contracture.

influence of certain general disease processes is seen in Table XXXVII. The cases analysed here are those in which the disease process concerned was the only one present. This table does not reveal a significant relationship between any general disease process and the incidence of lymphorrhages. The influence of certain factors in and near the muscles on the incidence of foci is seen in Table XXXVIII. The difference between the incidence of lymphorrhages in this group as a whole and in those blocks of muscle in which no such local factors were present is highly significant (P is less than .01).

The different groups of diseases were compared to see whether there was any difference in the size of the lymphorrhages (Table XXXIX), their histological distribution in the muscles (Table XL), and their number per unit piece of muscle (Table XLI). The number of foci per unit piece of muscle was obtained by measuring, as accurately as possible the area of each section and calculating the number of lymphorrhages per unit area. Since all the sections were cut at 4 μ, it was unnecessary to introduce the third dimension. The final figure used for comparison of cases was the average of the results for each individual block in that case. No significant differences were noted in the size and histological distribution of the foci. The number of foci per unit/

Table XXXVII.

Relationship between some General Disease Processes and the Incidence of Lymphorrhages in Skeletal Muscles in Non-rheumatic Diseases.

Disease Process	Total Cases	Positive Cases	
		No.	Per cent
x Inflammation	73	5	7
Chemical poisoning	1	0	0
+ General Ischaemia	21	0	0
Hepatic failure	1	0	0
Renal failure	6	0	0
Endocrine Disorders and Pregnancy	4	0	0
Tumours	28	3	11
• Trauma and Normal Individuals	24	1	4

x Includes all inflammation due to known organisms, those in which the causative organism was not identified, e.g., cholecystitis, and such non-specific inflammatory processes as peptic ulcer. Neither this group nor " tumours" include cases with local lesions in muscles examined.

+ Includes cardiac failure, severe anaemia, severe non-inflammatory respiratory disease and hypertension (unless complicated by uraemia).

• Includes cases in which death occurred within a week of an accident with no other lesions discovered at autopsy.

Table XXXVIII.

Influence of Local Factors on the Incidence of Lymphorrhages in Muscles in Non-rheumatic Diseases.

Diagnosis	Total Blocks	Positive Blocks	
		No.	Per cent
Inflammation	45	5	11
Atrophy	14	2	14
Degeneration, or necrosis	244	25	10
Muscular dystrophies	10	3	30
Tumour deposits	5	1	20
Local ischaemia	47	16	34
Venous thrombosis	5	0	0
Fibrosis	4	0	0
Total	374	52	14
Local factors absent	835	41	5

Table XXXIX.

Size of Largest Lymphorrhages in Skeletal Muscles.

	Total Cases	Logarithm of Size of largest Focus in micra².					
		3.0 to 3.9		4.0 to 4.9		5.0 plus	
		No.	Per cent	No.	Per cent	No.	Per cent
x Rheumatoid Arthritis	35	14	40	17	49	4	11
Other Rheumatic Diseases	22	7	32	12	35	3	14
Non-rheumatic Diseases	32	17	53	12	37	3	9
Total	89	38	43	41	46	10	11

x Includes only those cases in which there was no evidence of any other disease.

Table XL.

Histological Distribution of Lymphorrhages within Skeletal Muscles.

	Total Foci	Histological Site of Foci							
		Endomysial only		Perimysial only		Endo- and Perimysial		Epimysial	
		No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
x Rheumatoid Arthritis	75	48	64	25	33	1	1	1	1
Other Rheumatic Diseases	139	58	42	63	45	7	5	11	8
Non-rheumatic Diseases	161	81	50	56	35	5	5	16	10
Total	375	187	50	144	38	13	3	28	7

x Includes only those cases in which there was no evidence of any other disease.

Number of Lymphorrhages per Unit Piece of Muscle.

	Total Cases	Number of Foci per Unit Piece of Muscle							
		Nil		0.1 to 0.9		1 to 5		More than 5	
		No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
x Rheumatoid Arthritis	53	31	58	3	6	10	19	9	17
Other Rheumatic Diseases	68	47	69	7	10	13	19	1	1
Non-rheumatic Diseases	401	368	92	25	6	7	2	1	0.2
Total	522	446	85	35	7	30	6	11	2

x Includes only those cases in which there was no evidence of any other disease.

unit piece of muscle in rheumatoid arthritis is very significantly higher than that in the other two groups. This was reflected in the relative number of blocks in the different groups which contained foci (Table XLII).

Although the study of degeneration of muscle fibres was not one of the objects of this investigation, the occurrence of such changes throws some light on the aetiology of lymphorrhages. Table XLIII shows the incidence of waxy degeneration (Zenker's degeneration, Zenker's necrosis), vacuolation, fragmentation and necrosis in the three groups of patient studied. Degeneration was seen in as wide a variety of diseases as were lymphorrhages.

Other Focal Lesions.

This group includes all foci which failed to satisfy any of the criteria for lymphorrhages, or in which additional features were present. The most frequent variations were in cytology, such as the presence of polymorphs, plasma cells, histiocytes or subsarcolemmal nuclei in unusually high proportions (Figs. 156 -161) ; presence of giant-cells or red blood cells ; presence of Russell bodies (Fig. 156). Some foci were otherwise typical, but loose or diffuse and this feature was not due to artefact, such as the injection of local anaesthetic (Figs. 162-164). The group also includes otherwise typical lymphorrhages with infiltration of the media or intima of blood vessels (Fig./

Table XLII

Number of Blocks of Skeletal Muscles containing Lymphorrhages.

	Total Blocks	Positive Blocks	
		No.	Per cent
[x] Rheumatoid Arthritis	94	25	27
Other Rheumatic Diseases	214	49	23
Non-rheumatic Diseases	1182	76	6
Total	1490	150	10

x Includes only those cases in which there was no evidence of any other disease.

Table XLIII

Incidences of Degeneration in Skeletal Muscles.

	Total Cases	Positive Cases.	
		No.	Per cent
Rheumatoid Arthritis	93	16	17
Other Rheumatic Diseases	73	12	16
Non-Rheumatic Diseases	419	91	22
Total	585	119	20

Skeletal Muscle in Rheumatoid Arthritis.

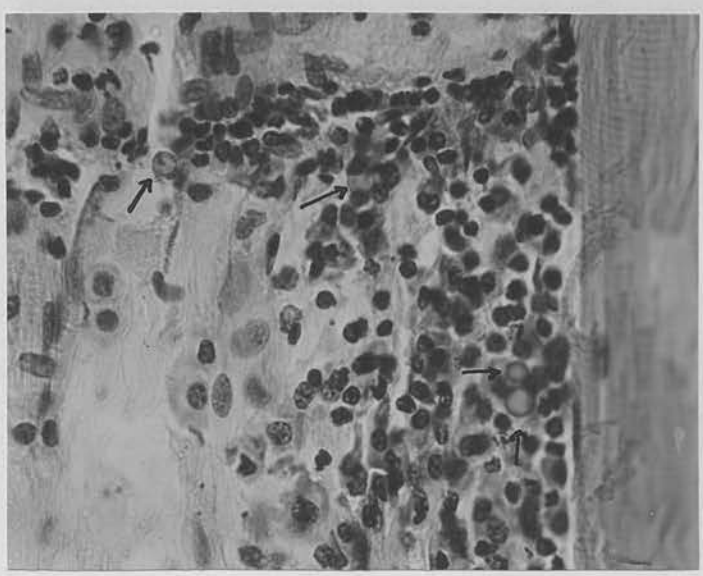

Fig. 156. Case 13 x 525. Deltoid.
Part of a large endomysial focus showing an unusually high proportion of plasma cells and subsarcolemmal nuclei. Russell bodies are associated with some of the former (arrows).

Skeletal Muscle in Scleroderma.

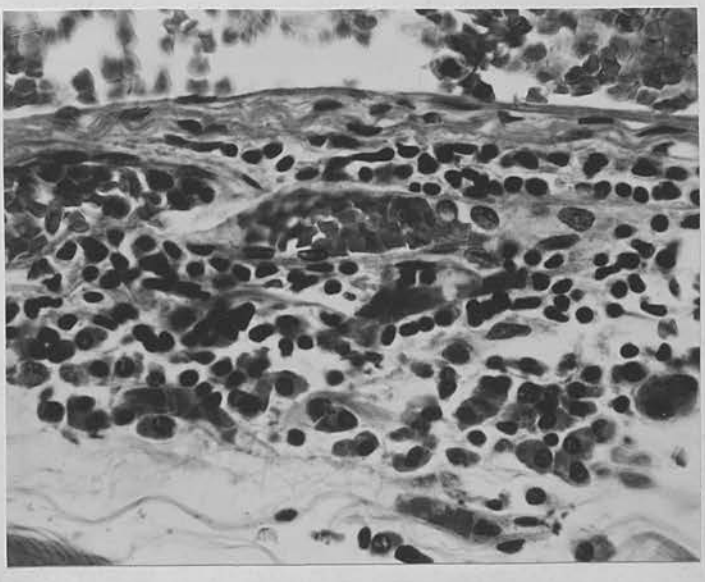

Fig. 157. Case 538 x 500.
Unusually high proportion of plasma cells in a perimysial focus. The patient also had healed rheumatic mitral endocarditis.

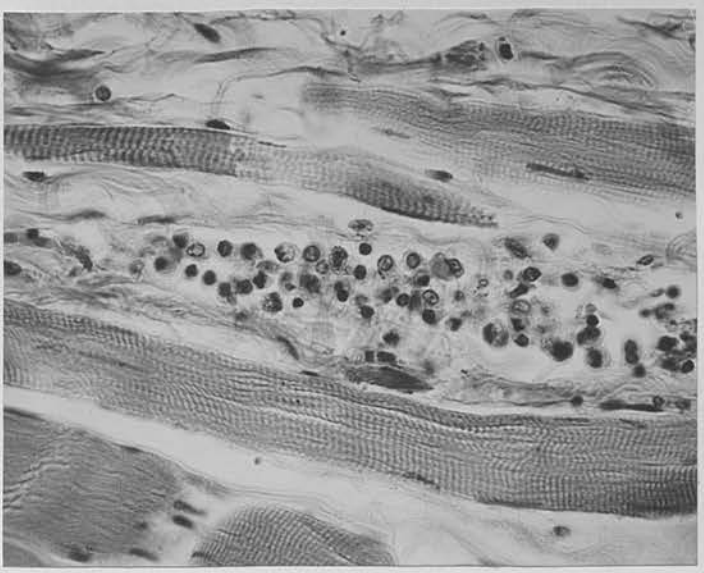

Fig. 158. Case 1067 x 350. Diaphragm.
Small, endomysial focus consisting mainly of histiocytes. Very early degenerative changes in adjacent muscle fibres but no necrosis. The patient had uraemia and congestive cardiac failure following hypertension.

Fig. 159. Case 1384 x 375.
Rather loose, endomysial focus with high proportion of histiocytes and polymorphs. Lymphorrhages were also present. The patient had focal necrosis in spleen and lymph nodes, healed serositis and congestive cardiac failure.

Skeletal Muscle in Rheumatoid Arthritis.

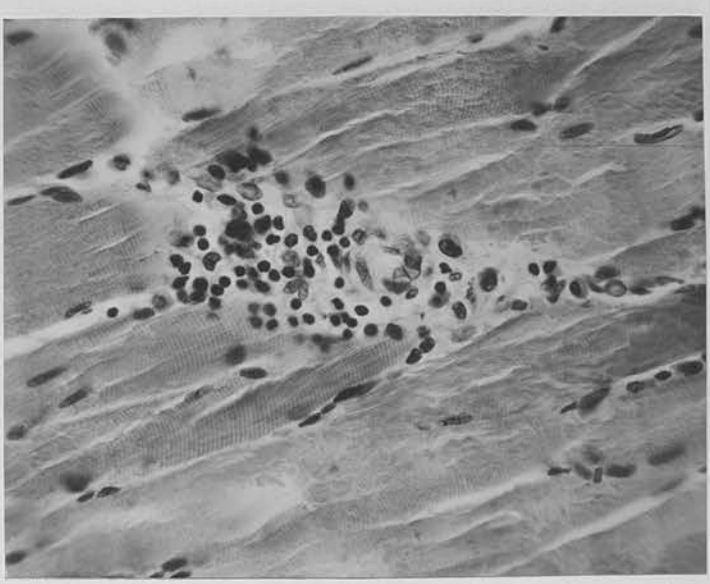

Fig. 160. Case 17 x 375. Diaphragm.
Small, endomysial focus with high proportion of subsarcolemmal nuclei. See also Figs. 165 and 166, p. 240. The patient died of acute liver necrosis following viral hepatitis and had a toxic reaction to gold three weeks before death.

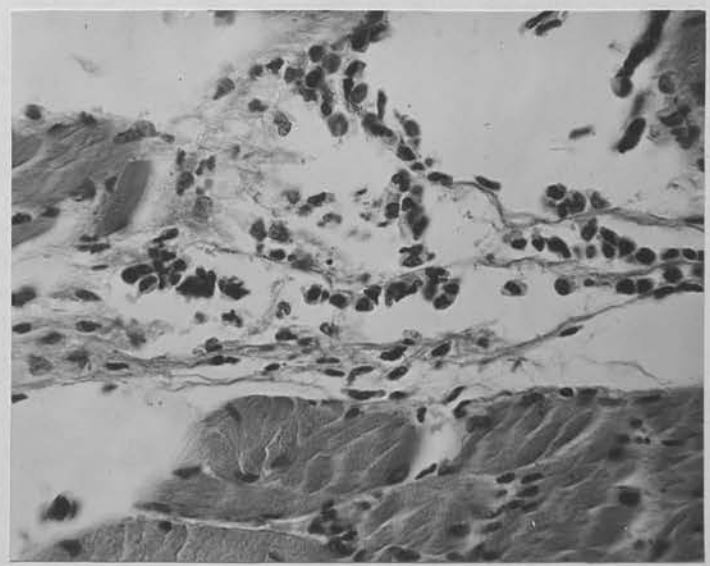

Fig. 161. Case 170 x 375. Diaphragm.
A small, loosely arranged, perimysial collection of lymphocytes and histiocytes.

Fig. 162. Case 1089 x 100. Diaphragm. Loosely arranged infiltration of lymphocytes in subserous region. Hyaline change in some nearby muscle fibres. The patient had a gastro-colic fistula and localised peritonitis elsewhere in abdomen.

Skeletal Muscle in Dermatomyositis.

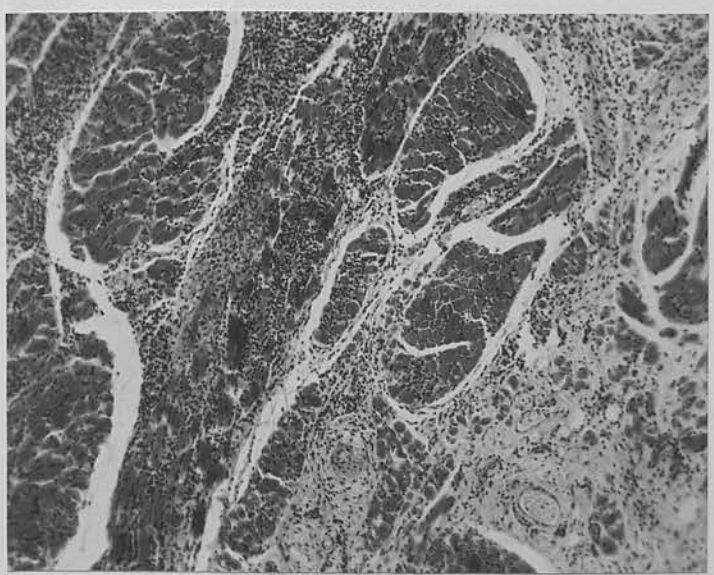

Fig. 163. Case 529 x 75. Tongue. Diffuse infiltration, mainly lymphocytic, with degeneration of muscle fibres to the left of centre and healing arteriolitis (below centre). The patient also had polyarteritis and streptococcal septicaemia.

Skeletal Muscle in Thyrotoxicosis.

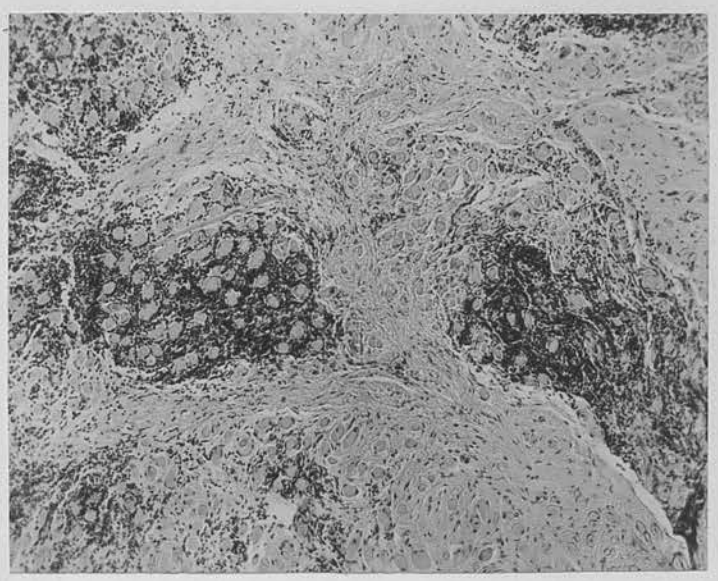

Fig. 164. Case 1241 x 75. External rectus. Diffuse infiltration with lymphocytes and fibrosis. The patient developed exophthalmic ophthalmoplegia following total thyroidectomy.

(Fig. 165), healed arteritis (Fig. 166) or primarily vascular lesions such as polyarteritis nodosa (167). Encapsulation (Fig. 168) or the presence of more than minimal quantities of collagen (Figs. 169 and 170), especially if this showed necrosis (Fig. 171) were other reasons for classifying foci in this group. It also includes foci which contained fibrin or blood-pigment (Fig. 172). The last reasons for including foci in this group were the presence of degenerate muscle fibres within a focus and degeneration or regeneration in adjacent muscle fibres (Figs. 173-175). The degeneration included those mentioned above (p. 231) and hyaline change. Care must be exercised in the interpretation of degeneration in specimens of muscle for these show many pseudo-degenerative fixation artefacts due to the contractility of the fibres (Meyenburg, 1929 ; Speidel, 1938, 1939). Focal lesions of clear-cut aetiology which were seen but not discussed further included pyaemic abscesses, tumour deposits, including intravascular cells in leukaemia (Fig.176), and intramuscular haemopoiesis (Fig. 177).

The incidence of all other focal lesions is given in Table XLIV. As with lymphorrhages the differences between the incidence in non-rheumatic diseases and those in rheumatoid arthritis and the other rheumatic diseases are significant (P is less than .01). The difference between the incidence/

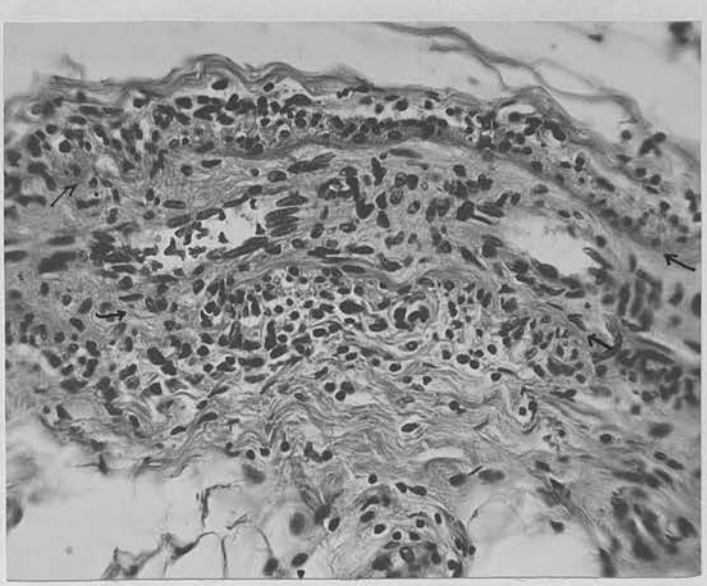

Fig. 165. Case 17 x 275. Pectoralis major. Subacute arteritis with intimal fibrosis. The arrows indicate the internal elastic lamina. Similar lesions were present in peripheral nerve (Fig. 198, p. 292) and heart (Figs. 222-225, pp. 336-337).

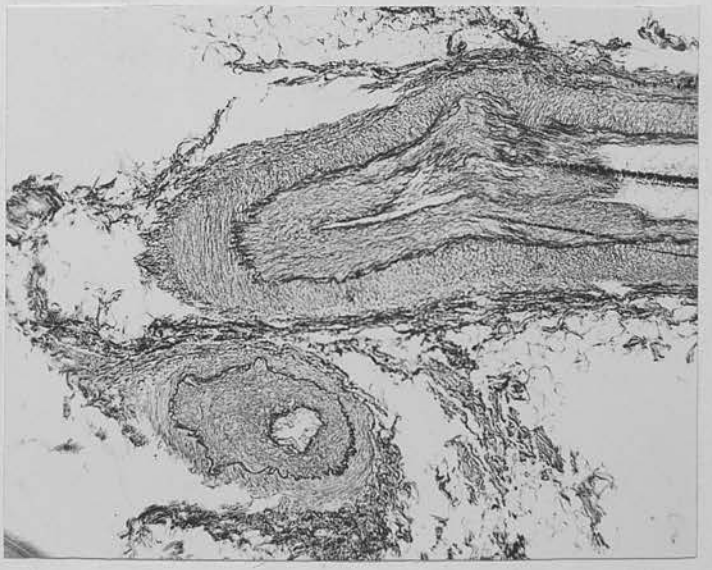

Fig. 166. Case 17 x 70. Further section from the same block, stained by Weigert's elastin method. Marked endarteritis obliterans of medium sized artery without destruction of elastic tissue.

Skeletal Muscle in Polyarteritis Nodosa.

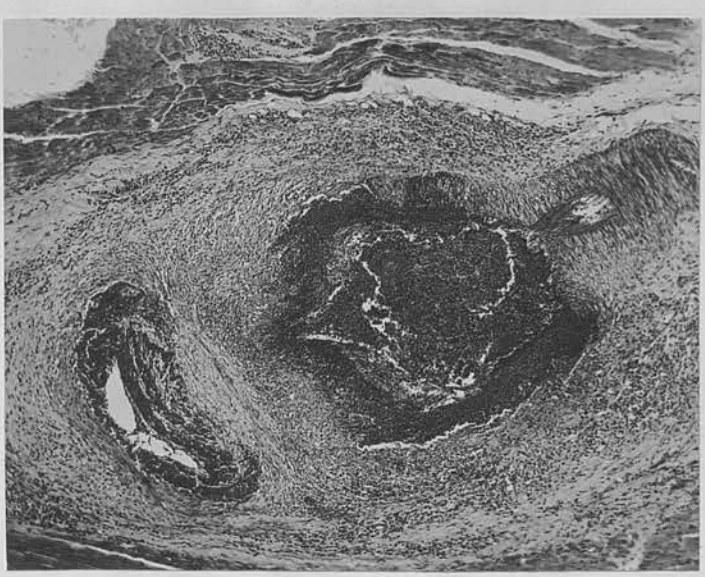

Fig. 167. Case 540 x 55. Relatively normal arterial wall at the upper right margin becoming necrotic with thrombosis and organisation towards the centre of the field. An apparently endomysial lymphorrhage is seen to the left of the upper margin (see text). Atrophy of muscle fibres.

Skeletal Muscle in Scleroderma.

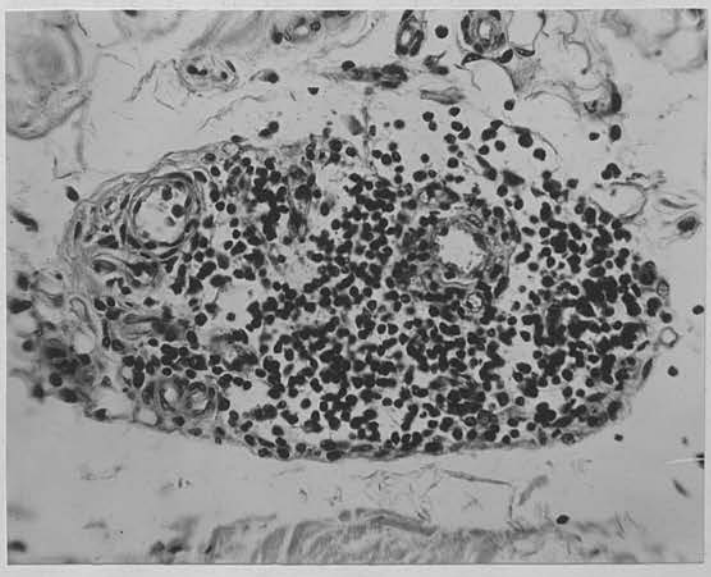

Fig. 168. Case 537 x 275. Partial encapsulation of an otherwise typical lymphorrhage.

Skeletal Muscle in Rheumatoid Arthritis.

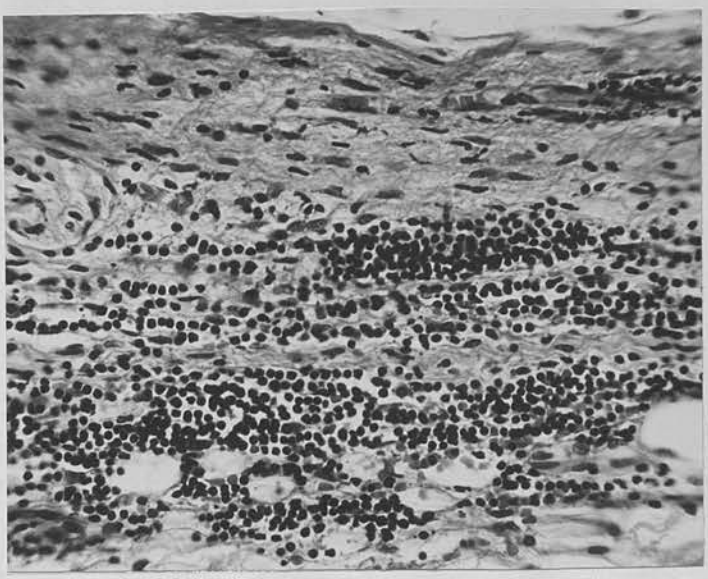

Fig. 169. Case 13 x 280. Rectus abdominis. Part of a large, perimysial focus of typical cytology, but containing an excessive amount of fibrous tissue.

Skeletal Muscle in Rheumatic Fever.

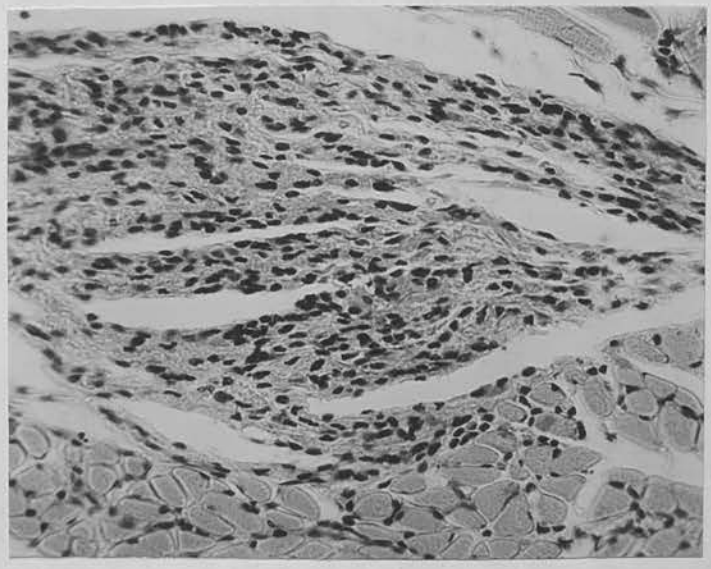

Fig. 170. Case 251 x 275. Pharyngeal muscle. A healing Aschoff body.

Skeletal Muscle in Systemic Lupus Erythematosus.

Fig. 171. Case 526. x 180. Rectus abdominis. Marked swelling, eosinophilia and fragmentation of collagen. Degeneration of muscle fibres with proliferation of subsarcolemmal nuclei. Focal and diffuse round cell infiltration. Lymphorrhages were also present.

Skeletal Muscle in Polyarteritis Nodosa.

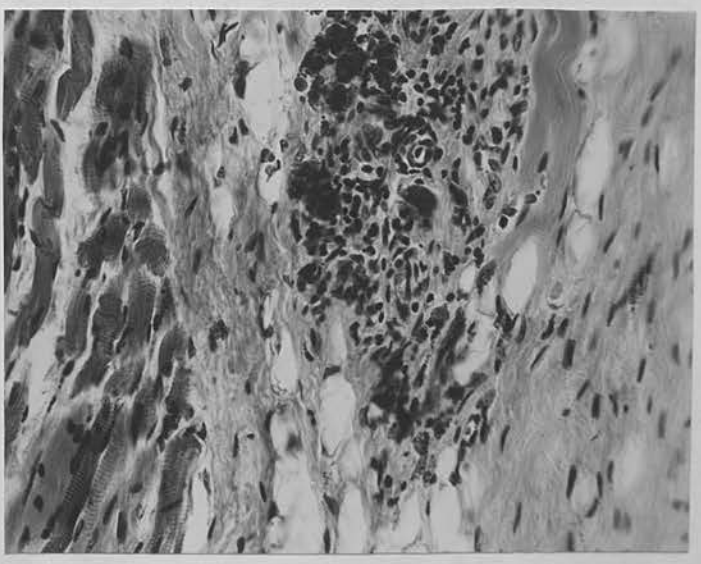

Fig. 172. Case 540 x 250. Haemosiderin pigment in histiocytes in a focus close to a healed arterial lesion.

Skeletal Muscle in Immersion Foot.

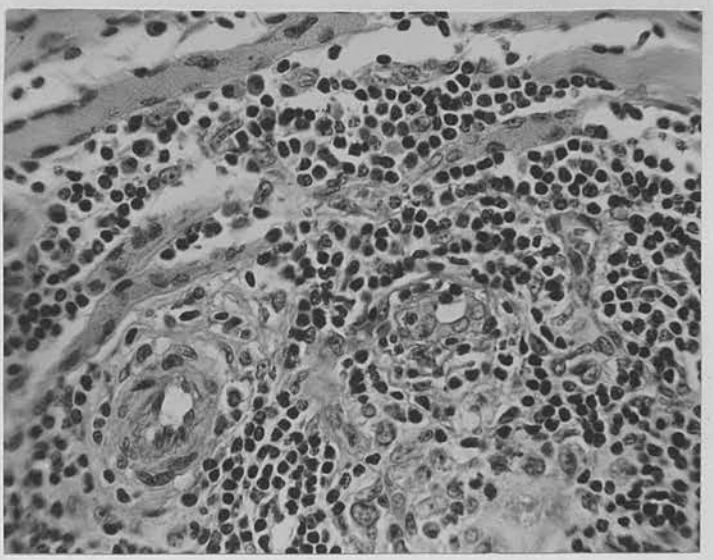

Fig. 173. Case 1226 x 375. Degenerating muscle fibres in and around a focus which also shows endothelial swelling in arterioles and groups of large histiocytes.

Skeletal Muscle in Rheumatoid Arthritis.

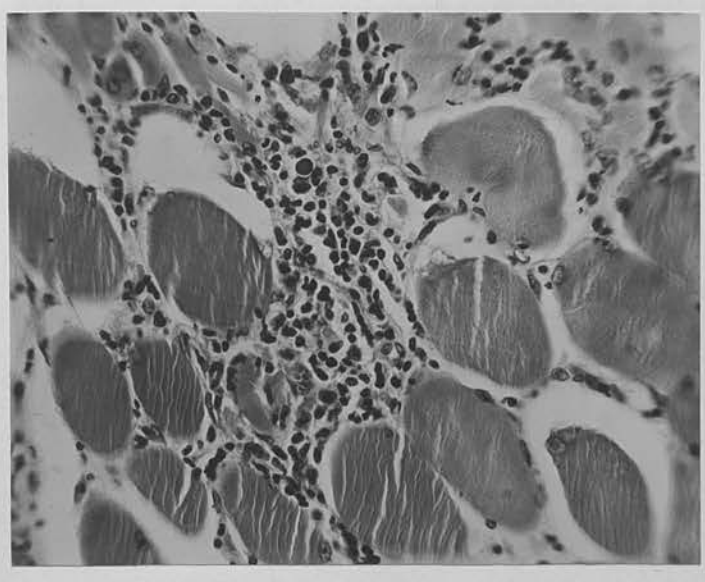

Fig. 174. Case 14 x 275. Quadriceps. Endomysial focus with degenerating muscle fibres seen in cross section. The patient also had Parkinsonism.

Skeletal Muscle in Rheumatoid Arthritis.

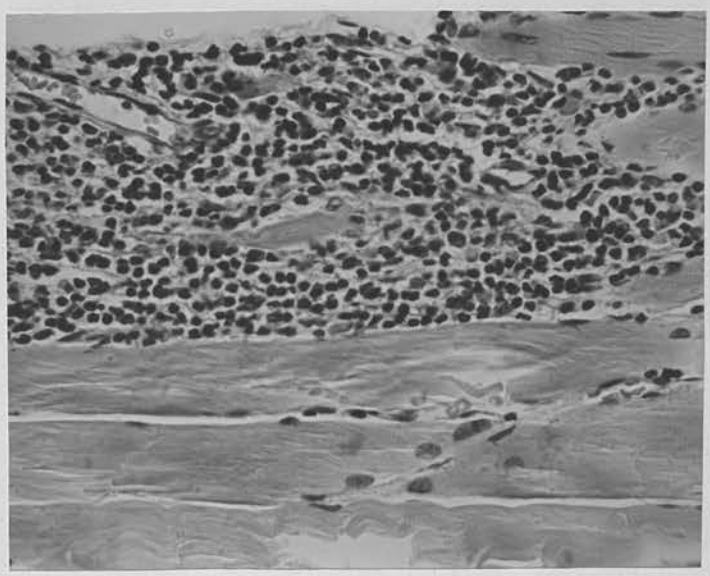

Fig. 175. Case 153 x 325. Extensor of wrist. Otherwise typical focus containing a degenerating muscle fibre.

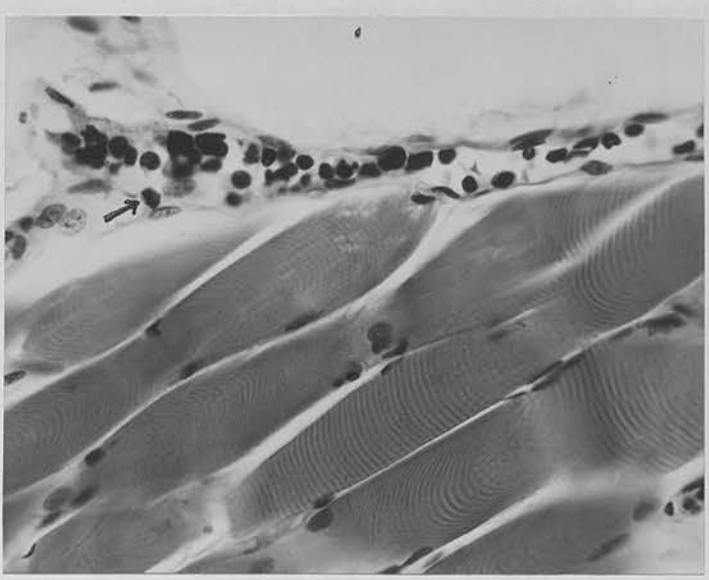

Fig. 176. Case 1100 x 450. Pectoralis major. Lymphocytes and lymphoblasts, one in mitosis, within a distended lymphatic in a case of acute lymphatic leukaemia.

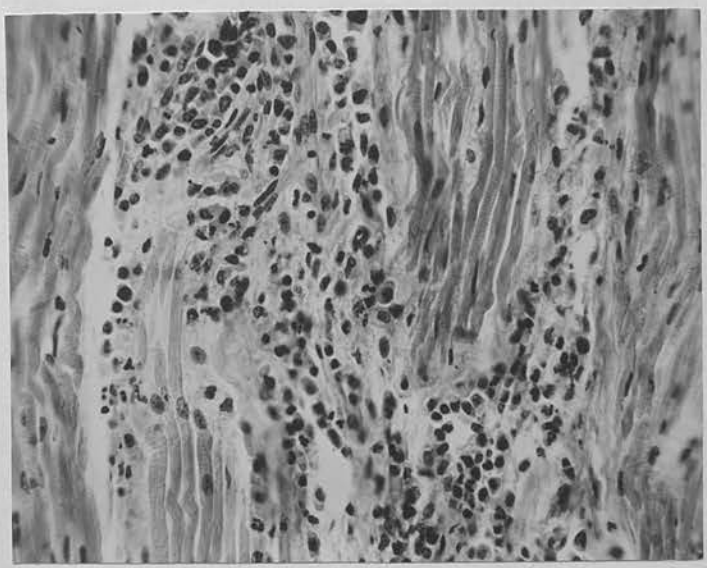

Fig. 177. Case 1144 x 275. Rectus abdominis. Haemopoiesis in a male infant with erythroblastosis foetalis.

Table XLIV.

Incidences of Other Focal Lesions in Skeletal Muscles.

	Total Cases	Positive Cases	
		No.	Per cent
Rheumatoid Arthritis	x 93	16	17
Other Rheumatic Diseases	73	22	30
Non-rheumatic Diseases	419	32	8
Total	585	70	12

x Includes the same cases as Table XXV, the following being positive - one autopsy case with mitral stenosis and one autopsy case with acute rheumatic carditis.

cidence in rheumatoid arthritis and that in the her rheumatic diseases is also significant, but a lesser extent (P is less than .02). The cidence of other focal lesions in the individual her rheumatic diseases is given in Table XLV.

DISCUSSION.

Examination of this large series of cases has iled to reveal any focal lesion which is specific rheumatoid arthritis. The lesions found in at disease were lymphorrhages, minor variations erefrom and, occasionally, subacute arteritis. mphorrhages were seen in some other rheumatic seases, such as systemic lupus erythematosus d scleroderma,more often than in rheumatoid thritis (Table XXXIII) and the incidence in all her rheumatic diseases as a group was not gnificantly less than that in rheumatoid thritis (Table XXV). They were also seen in arly fifty non-rheumatic diseases of widely ffering nature, such as tuberculosis, poliomyelit-, malignant tumours, cirrhosis of the liver, phrosclerosis and diabetes mellitus (Table XXXVI). ey were even seen in a stillborn anencephalic etus and in apparently normal individuals. sions showing minor variations from lymphorrhages re seen in the same wide distribution as lympho-hages themselves. These results support those Clawson et al (1947) and Sokoloff et al (1950).

Lymphorrhages of all sizes and in all

Table XLV

Incidences of Other Focal Lesions in Skeletal Muscles in Other Rheumatic Diseases.

Diagnosis	Total Cases	Positive Cases	
		No.	Per cent
Ankylosing spondylitis	6	0	0
Osteoarthritis	9	1	11
Gout	1	0	0
[X]Rheumatic fever	32	5	16
Systemic lupus erythematosus	5	5	100
[X]Polyarteritis nodosa	8	6	75
[X]Dermatomyositis	7	3	43
[X]Scleroderma	5	2	40
Total	73	22	30

x = includes the same cases as Table XXXIII, the following being positive :- one case of subacute bacterial endocarditis, one of dermatomyositis with polyarteritis and one of scleroderma with mitral fibrosis.

seases showed the same histological structure. ere was no evidence of a progressive series of anges such as is seen in the tubercle or the choff body. Nor was any evidence of a healing resolving stage seen, even in those cases of active rheumatoid arthritis where they were esent. Furthermore, the number of lymphorrhages r unit volume in different blocks from the same se varied considerably. Great care must be ken, therefore, in attributing minor variations the histological structure of these lesions, as en in serial biopsies, to the effect of any ug (Norcross et alii, 1950 ; Giansiracusa et ii, 1951). The same care is necessary in the e of muscle biopsy to assess improvement in lyarteritis nodosa, for the lesions of this sease are subject to considerable natural riation. Two of the cases of systemic lupus ythematosus had been treated with ACTH/and showed shortly before the muscles were studied rked clinical improvement while receiving the drug. neither case did the lesions in muscle show gns of healing : indeed, in one case the muscle sions were the most severe seen in all the cases the disease.

Although not specific to rheumatoid arthritis, mphorrhages were sufficiently common in that sease to suggest a causal relationship (Table XXVI). rthermore, they were more readily found in that sease than in any other disease (Table XLI). tailed analysis of those cases of rheumatoid thritis/

arthritis in which there was no evidence of any other disease failed to reveal any definite correlation with the age of the patient (Table XXVIII), the duration (Table XXIX) and activity (Table XXX) of the disease or the source of the specimen in relation to affected joints (Table XXXII). Although not significant the relationship between the incidence of foci and the stage of the disease showed a definite tendency towards increasing frequency with increased damage to joints, which were more readily seen when all cases of rheumatoid arthritis were analysed, regardless of the presence or absence of other pathological processes. (Table XXXII). The presence of foci was not correlated with the hyperplasia of lymphoid tissues which sometimes accompanies the disease. Thus, the case of 'Felty's Syndrome ' showed only a single, very small focus in one of the three blocks examined, whereas, in the case which showed the most marked involvement of muscles, the lymph nodes and spleen were normal. A case of juvenile rheumatoid arthritis examined at autopsy subsequent to the study of this series showed hyperplasia of lymph nodes and spleen but only one lymphorrhage was found in blocks from five muscles. Few of the cases of the other rheumatic diseases showed hyperplasia of lymphoid tissues, although these tissues might be involved in the disease, e.g., infarcts of the spleen in polyarteritis nodosa and degeneration of lymphoid/

lymphoid tissue in systemic lupus erythematosus. Yet in several of these cases, involvement of muscle was nearly as marked as in rheumatoid arthritis.

No significant correlations were found which indicated the factors responsible for the occurrence of lymphorrhages in non-rheumatic diseases, but certain suggestive findings were obtained. Lymphorrhages were more common in the presence of local factors, such as ischaemia and muscular dystrophies, than in the absence of such factors (Table XXXVIII). It should be noted however, that the presence of the foci was not closely related to the degree, or extent of degeneration in muscle fibres (compare Tables XXVI and XLIII). Thus in Weil's disease, where degeneration was nearly always severe and widespread, lymphorrhages were rare. Degeneration and atrophy were frequently present in other conditions without any cellular reaction, which was usually seen only when necrosis had occurred. In such circumstances the cells were mainly histiocytes and, in contrast to the cells in lymphorrhages, lay in the line of, rather than between, the muscle fibres (Fig. 178). As the routine haematoxylin and eosin technique is relatively crude, it is possible that it failed to reveal minor degrees of damage to muscle fibres.

The presence of lymphorrhages near damaged muscle is in keeping with the occurrence of similar foci/

Skeletal Muscle in Weil's Disease.

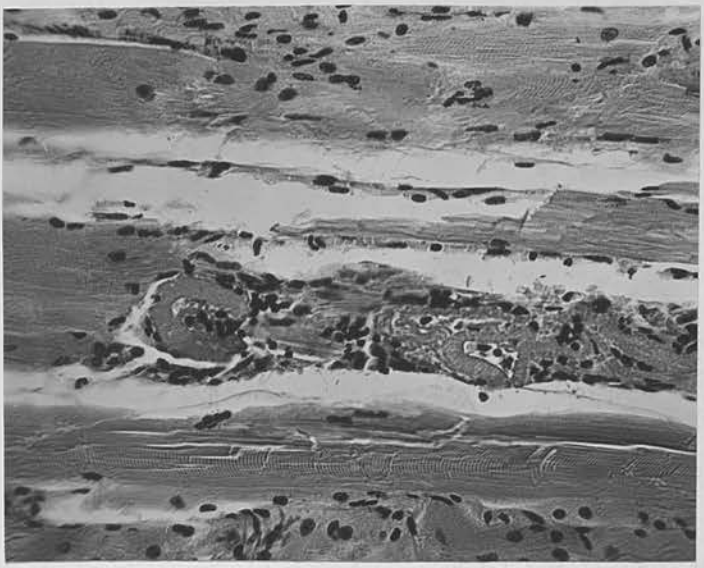

Fig. 178. Case 1249 x 250. Gastrocnemius. Necrosis of segment of muscle fibre, with lymphocyte and histiocyte reaction, the cells lying in the line of the fibre. Compare with Fig. 143, p. 202. The patient also had a duodenal ulcer and carcinoid tumours of the ileum.

foci in other tissues which are the site of non-inflammatory pathological processes, e.g., the thyroid in thyrotoxicosis and the breast in cystic hyperplasia. It possibly represents a non-specific reaction to locally released chemicals. A similar mechanism may be at work in the muscles in those cases in which the above-mentioned factors are present, even when damage is not demonstrable in histological sections. The presence of round cell foci in other tissues is not unknown even in the absence of local pathological processes, for foci are not infrequently seen in apparently healthy epicardium (Fig. 179), renal pelvis and suprarenal glands. Similar lesions also have been described very recently in a high proportion of otherwise normal human pituitaries by Shanklin (1951) who regarded them as embryological in origin.

It would appear that biopsy of a single piece of skeletal muscle has a limited value in the diagnosis of rheumatic diseases. Certain lesions such as the Aschoff body, and the fully developed vascular lesions of polyarteritis nodosa are sufficiently characteristic to be diagnostic. (So too, is the urate deposit of gout which was not seen in this series, but has been described in skeletal muscle by Horwitz, 1949 (c)). These lesions were not found in every block of muscle taken at autopsy from cases of these diseases in which the diagnosis was proved by examination of other/

Lymphorrhage in Epicardial Tissue.

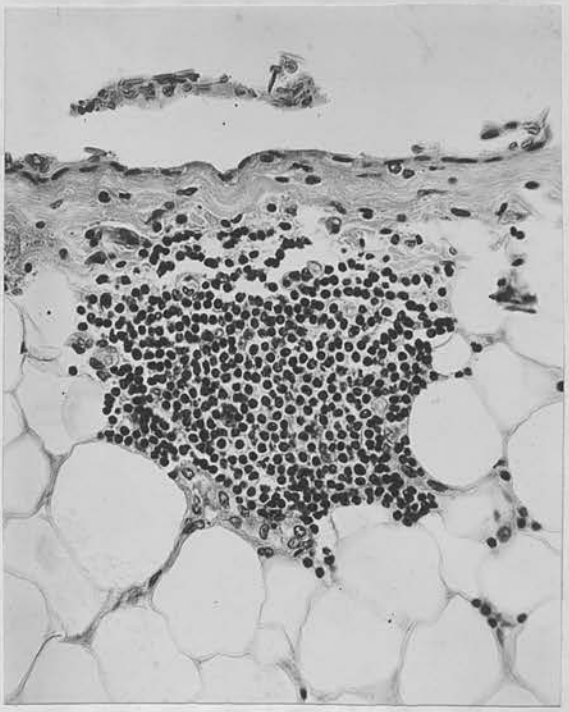

Fig. 179. Case 1170 x 275. Interventricular septum. Lymphorrhage just beneath epicardium. The patient had chronic pulmonary tuberculosis and Addison's disease due to tuberculosis of suprarenals. No other lesions were found in the heart.

other tissues. Therefore, their absence in a single biopsy specimen does not exclude the diagnosis.

The mere presence of lymphorrhages was of little diagnostic value for, in one or more muscles from some cases of other rheumatic diseases, they were the only lesion found. They were, however, more numerous in rheumatoid arthritis than in other conditions (see Table XLI), a feature which was also noted by Sokoloff et alii. The size (Table XXXIX) and histological site of the foci (Table XL) was of no value in differential diagnosis. The anatomical site from which the muscle was taken did not significantly influence the likelihood of finding lesions (Table XXVII). Although Aschoff bodies were found only in peritonsillar and pharyngeal muscles, they have been described in many other skeletal muscles (Gräff, 1927 ; Brogsitter, 1928 ; Sarafoff, 1932 ; Klinge, 1931(a), 1933(e)). Autopsy material was available from cases of rheumatoid arthritis and all the other rheumatic diseases. In one or more case of each disease, lymphorrhages or other focal lesions were found in all the muscles selected for study.

Study of the cases of dermatomyositis and scleroderma included in this series indicated that in some specimens from either disease contained only lymphorrhages. In scleroderma, all round cell infiltration was focal, the lesions other than lymphorrhages/

lymphorrhages seen differing from them only in minor details. On the other hand, some specimens from dermatomyositis showed diffuse infiltration (Fig. 163). This type of infiltration was not peculiar to dermatomyositis, being seen in thyrotoxicosis (Fig. 164). Degeneration and regeneration of muscle fibres was more marked in dermatomyositis than in scleroderma. These results are in agreement with those of workers who maintain that the two diseases are entities (Meyenburg, 1929 ; Keil, 1940 ; Brock, 1944). Recent or healed arteritis was seen in some cases of both diseases. In three cases of systemic lupus erythematosus, a combination of necrosis of collagen, marked degeneration of muscle fibres, mainly in the form of vacuolation and hyaline change, with lymphorrhages was seen which was not met in any other disease. Steiner (1948) was also able to differentiate the lesions in lupus from those in other diseases.

SUMMARY.

1. The literature on focal round cell lesions (lymphorrhages) in skeletal muscles has been reviewed. Their existence has been known in several diseases for many years, but their significance has not been investigated in detail until recently, when similar lesions were claimed to be specific to rheumatoid arthritis. This opinion/

opinion has been disputed. An attempt has been made recently to see whether the dramatic clinical improvement in rheumatoid arthritis on treatment with cortisone is associated with any change in the histology of muscle.

2. The objects of this study were a) to determine whether a focal lesion specific to rheumatoid arthritis occurs in the skeletal muscles. b) to attempt to determine the factor, or factors, responsible for the occurrence of lymphorrhages in skeletal muscles. c) to ascertain the value of biopsy of a single piece of skeletal muscle in the diagnosis and of serial biopsies in the assessment of the effects of drugs in rheumatic diseases.

3. Skeletal muscles have been examined for the presence of focal lesions from 93 cases of rheumatoid arthritis, 73 of other rheumatic diseases and 419 of non-rheumatic diseases. Twenty four of the cases of rheumatoid arthritis, 53 of the other rheumatic diseases and 246 of the other rheumatic diseases were studied at autopsy, blocks being taken from several muscles in each case. The remaining specimens were obtained at biopsy when one or two blocks were taken.

4. No lesion specific to rheumatoid arthritis was seen. The lesions found in that disease were lymphorrhages, other focal lesions showing minor variations therefrom and, occasionally, subacute/

subacute arteritis. These lesions were all found in other rheumatic diseases. Lymphorrhages were found in nearly 50 widely different non-rheumatic diseases. The incidence of lymphorrhages was 42% in rheumatoid arthritis, 33% in other rheumatic diseases and 8% in non-rheumatic diseases.

5. Although the incidence of lymphorrhages in rheumatoid arthritis is significantly higher than in non-rheumatic diseases, it could not be correlated with age, duration, activity or stage of the disease, the source of the tissue examined in relation to lesions in other tissues, or the hyperplasia of lymphoid tissue which sometimes accompanies that disease.

6. Apart from the rheumatic diseases and myasthenia gravis, no individual disease or group of diseases was associated with a significantly high incidence of lymphorrhages. In the non-rheumatic diseases, a higher incidence occurred in the presence of local lesions in, or near, the muscles than in their absence. Lymphorrhages appear to be a non-specific reaction to locally released chemicals, rather than a reaction to some general factor, such as a circulating toxin.

7. Biopsy of a single piece of skeletal muscle is of limited value in the diagnosis of chronic rheumatic diseases. Lesions sufficiently characteristic to be diagnostic were found in some cases of rheumatic fever, polyarteritis nodosa/

nodosa and systemic lupus erythematosus. Lesions which, though not peculiar to the disease, were suggestive were found in some cases of dermatomyositis. The site of biopsy did not influence the likelihood of finding lesions in these diseases.

8. It is extremely doubtful whether serial biopsies of skeletal muscle are of value assessing the effects of drugs in chronic rheumatic diseases.

SECTION V.

Focal Lesions in Peripheral Nerves in Rheumatoid Arthritis and Other Conditions.

INTRODUCTION.

Pathological study of the nervous system in rheumatoid arthritis has been much less intensive than that of the other tissues discussed in this thesis. Most early workers were concerned mainly with attempting to demonstrate in the spinal cord lesions responsible for, or associated with the marked muscular atrophy which is a feature of the disease. Morrison et al (1947) discussed several papers on this subject which appeared between 1893 and 1913. Freund et al (1942) appear to have been the next to study the nervous system, turning their attention to peripheral nerves after failing to find " specific or characteristic lesions in the brain or spinal cords. " They found nodular granulomatous lesions in three out of five cases and regarded them as specific, since similar lesions were not present in any of the 84 non-rheumatic controls which they studied. Lesions which could be differentiated from the focal lesion of rheumatoid arthritis were seen in Parkinsonism, thromboangiitis obliterans, bronchial carcinoma and dermatomyositis. The lesions in the nerves in rheumatoid arthritis are essentially similar to those described later in muscles by the same group (Steiner et al, 1946). Indeed it was the presence of lesions in fragments

of muscle attached to a piece of nerve which led to the second investigation.

Morrison et al (1947, 1949) confirmed these findings in rheumatoid arthritis, but did not examine any controls. A search of the literature reveals that focal collections of round cells in peripheral nerves has been described in rheumatic fever (Koeppen, 1932), porphyria (Mason et al, 1933) and thromboangiitis obliterans (Barker, 1938) and that the lesions described by these workers were very similar to those claimed to be specific to rheumatoid arthritis. In view of the non-specific nature of the muscle lesions in rheumatoid arthritis discussed above it was decided to investigate peripheral nerves from a series of cases.

The objects of this study were a) to determine whether a focal lesion specific to rheumatoid arthritis occurs in peripheral nerves and to see whether any further light could be thrown on the factors responsible for the occurrence of lymphorrhages and b) to study the comparative incidences of lymphorrhages in muscles and nerves

MATERIAL AND METHOD.

Blocks of peripheral nerve were obtained at autopsy, with the exception of a few cases of osteoarthritis and thromboangiitis obliterans in which amputations were performed. Tissue was obtained from 20 cases of rheumatoid arthritis, 21 of/

of other rheumatic diseases and 120 unselected routine autopsies. The average number of blocks studied per case in the three groups was eight, six and five respectively. Long segments of femoral nerve and brachial plexus were removed in most cases. In a few cases blocks were taken from the sciatic, posterior tibial or anterior tibial nerves. Consecutive blocks about 2 cm. long were taken from each. The blocks were embedded in paraffin and cut longitudinally. In a few cases extra blocks were cut transversely. Single sections were cut and stained with haematoxylin and eosin. Serial sections were obtained and extra stains such as Masson's trichrome and van Giesons stain used when necessary.

RESULTS.

The incidence of all focal lesions is shown in Table XLVI. As in the case of skeletal muscles, these lesions were divided into two groups - lymphorrhages and other focal lesions. The various lesions resembled those in the muscles very closely, so they will not be described in detail again.

Lymphorrhages.

Lymphorrhages were most frequently epineural, in the loose connective tissue between nerve fascicles (Fig. 180-182) or perineural, impinging on, or lying between, the dense concentric layers of/

Table XLVI.

Incidences of all Focal Lesions in Peripheral Nerves.

	Total Cases	Positive Cases	
		No.	Per cent
* Rheumatoid arthritis	20	15	75
Other Rheumatic Diseases	21	12	57
Non-rheumatic Diseases	120	21	17
Total	161	48	30

* Includes 3 cases with pathological features of rheumatic heart disease (2 positive).

Normal Peripheral Nerve.

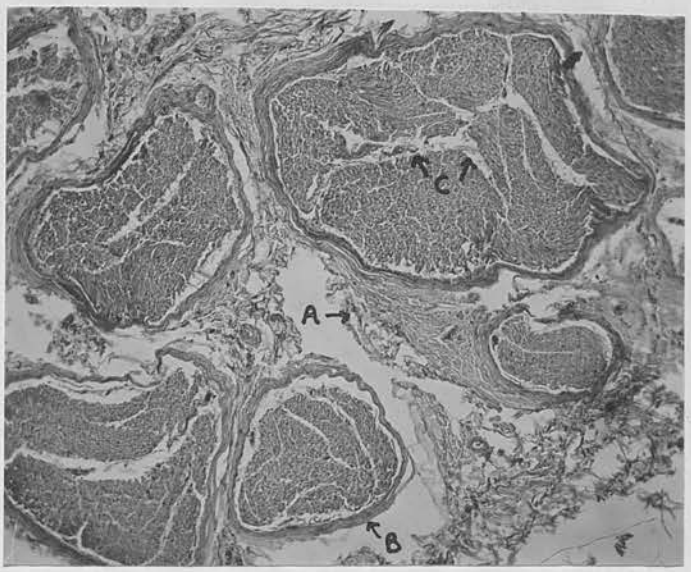

Fig. 180. x 50.
Cross-section showing distribution of connective tissue as epineurium (A), perineurium (B), and endoneurium (C).

Peripheral Nerves in Thromboangiitis Obliterans.

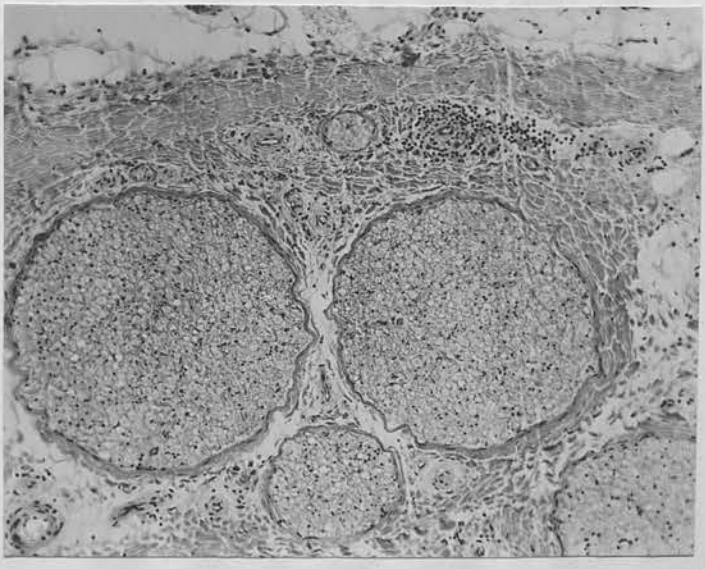

Fig. 181. Case 1267. x 100. Posterior tibial nerve. Small epineural lymphorrhage in cross section.

Peripheral Nerve in Mitral Stenosis.

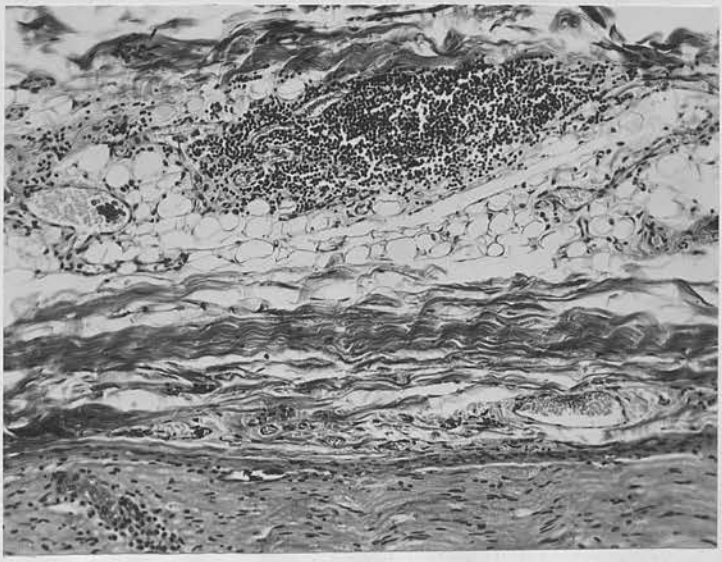

Fig. 182. Case 287 x 100. Femoral nerve. Fairly large, epineural lymphorrhage in longitudinal section, also slight cuffing of endoneural capillaries (bottom left).

of fibrous tissue investing the fascicles (Fig. 180, 183-187). Occasionally they were endoneural, lying between the nerve fibres themselves (Fig. 180, 188, 189). The histological distribution of lymphorrhages in nerves is shown in Table LVII. Because of the nature of the perineurium, foci in it often contained more fibrous tissue than foci in the other sites in nerves or any of the foci in muscle (Fig. 186). The shape was less variable than in the muscles, nearly all the foci being spindle-shaped. The cytology was the same as in the muscles except that central degeneration of lymphocytes was not seen and neurilemmal nuclei took the place of muscle nuclei (Figs. 189-191).

The incidences of lymphorrhages in peripheral nerves in rheumatoid arthritis, other rheumatic diseases and non-rheumatic diseases is shown in Table XLVII. The differences between the incidence in non-rheumatic diseases and those in rheumatoid arthritis and other rheumatic diseases respectively are significant (P is less than .01, using Yates' correlation). The difference between the incidence in rheumatoid arthritis and that in other rheumatic diseases is not significant (P is less than .20, using Yates' correction).

Factors Responsible for the Occurrence of Lymphorrhages in Peripheral Nerves.

The number of cases investigated in this study is too small for so extensive an analysis as was made/

Peripheral Nerve in Hypertension.

Fig. 183. Case 1470 x 100. Femoral nerve. Small, perineural lymphorrhage, partially surrounding an arteriole which shows marked arteriosclerosis.

Peripheral Nerve in Rheumatoid Arthritis.

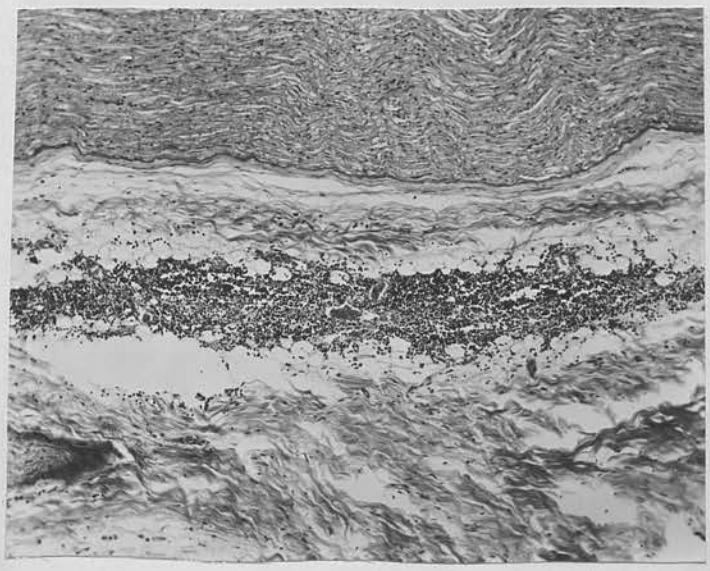

Fig. 184. Case 13 x 85. Femoral nerve. Large lymphorrhage impinging on perineural connective tissue and containing congested capillaries. See also Fig. 190, p. 271 ; Fig. 195, p. 290.

Peripheral Nerve in Carcinoma of Stomach.

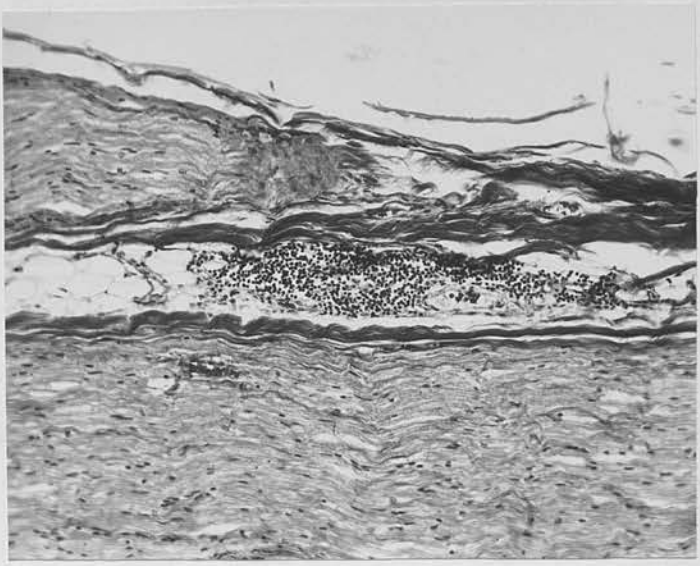

Fig. 185. Case 1395 x 100. Small lymphorrhage splitting up perineural connective tissue.

Peripheral Nerve in Rheumatoid Arthritis.

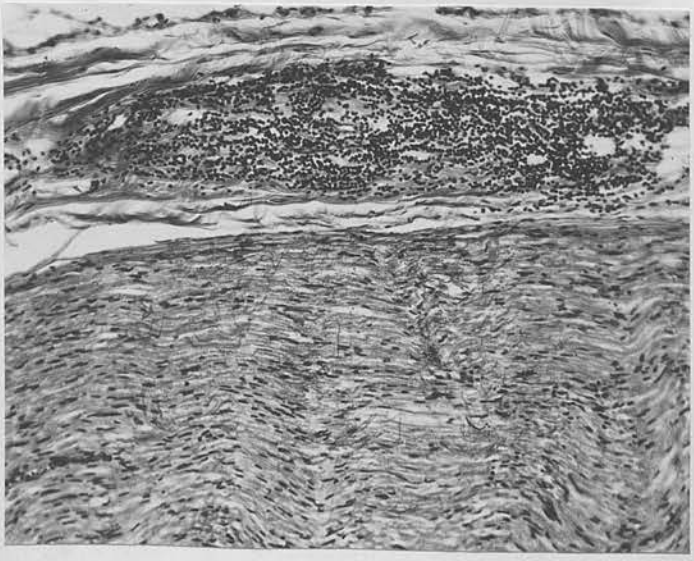

Fig. 186. Case 12 x 100. Lymphorrhage splitting perineural connective tissue and containing more collagen than perimysial foci. See also Fig. 196. The patient also had hypertension.

Peripheral Nerve in Rheumatoid Arthritis.

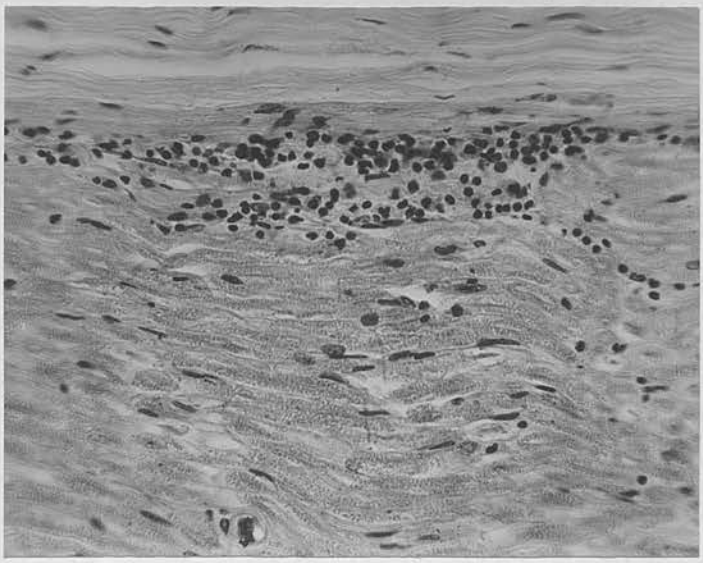

Fig. 187. Case 8 x 250. Small lymphorrhage lying between perineurium (above) and nerve fibres (below).

Peripheral Nerve in Myasthenia Gravis.

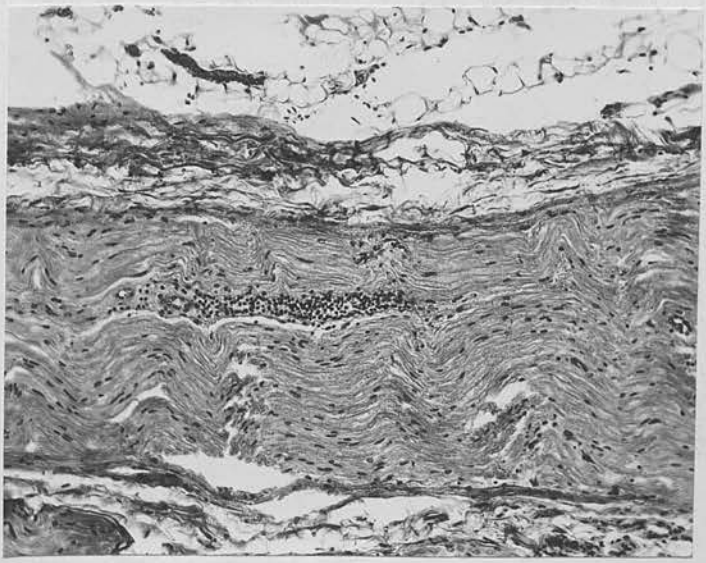

Fig. 188. Case 1370 x 100.
Small, endoneural lymphorrhage.

Peripheral Nerve in Rheumatoid Arthritis.

Fig. 189. Case 25 x 250. Brachial plexus. Small endoneural lymphorrhage. The clump of large cells to the left of centre is capillary endothelium. The patient also had acute rheumatic carditis.

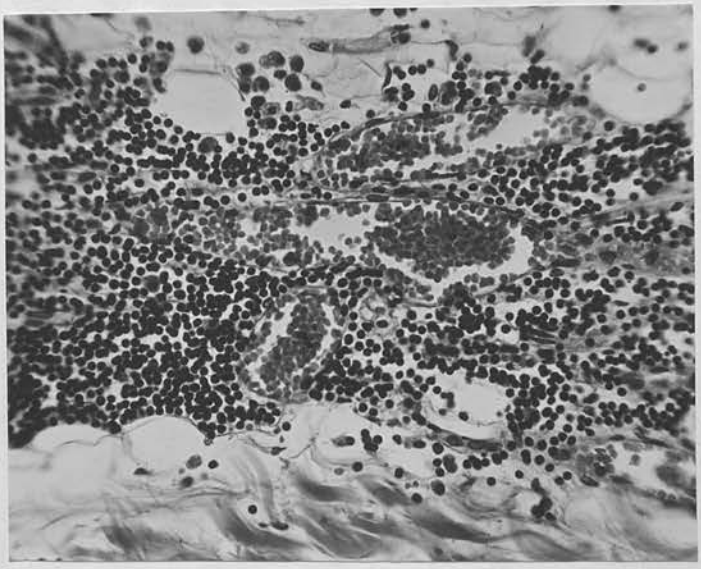

Fig. 190. Case 13 x 250. Central part of the focus in Fig. 184. The focus consists of lymphocytes and peripheral plasma cells and contains several congested capillaries.

Peripheral Nerve in Rheumatoid Arthritis.

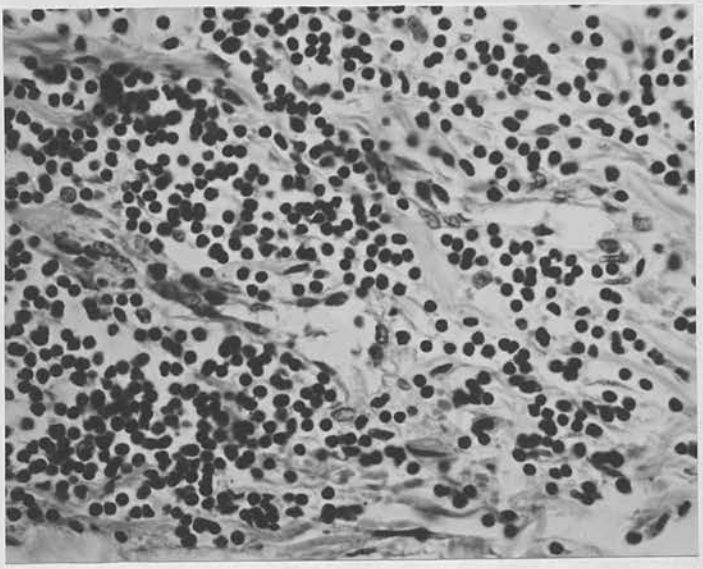

Fig. 191. Case 2 x 420. Brachial plexus. Part of a large, epineural lymphorrhage. The large " epithelioid " cells (left centre) are capillary endothelium. See also Fig. 194, p. 290. The patient also had amyloidosis.

Table XLVII.

Incidences of Lymphorrhages in Peripheral Nerves.

	Total Cases	Positive Cases	
		No.	Per cent
* Rheumatoid Arthritis	20	14	70
Other Rheumatic Diseases	21	9	43
Non-Rheumatic Diseases	120	18	15
Total	161	41	25

* Includes the same cases as Table XLVI, two cases being positive.

made in Section IV of the thesis. Indeed, in most of the following tables the number of observations recorded is so small that no definite conclusions can be made. Furthermore, none of the cases of rheumatoid arthritis was without evidence of other pathological processes, so that the results given are not strictly comparable with those shown for the corresponding factors in the case of the skeletal muscles.

The age-incidences in rheumatoid arthritis are shown in Table XLVIII and the influence of the activity and stage of the disease in Tables XLIX and L respectively. The incidences in the individual other rheumatic diseases are shown in Table LI and the age-incidences in the whole group of other rheumatic diseases in Table LII. The age-incidences in the non-rheumatic diseases are given in Table LIII. Table LIV contains an alphabetical list of the individual diseases which, singly or in different combinations were associated with foci. The influence of certain general disease processes, which were the only lesions present in the cases analysed is seen in Table LV. No significant relationship occurred. As in the skeletal muscles, no significant differences were noted in the size (Table LVI) and histological distribution of the foci (Table LVII). The number of foci per unit piece of nerve was significantly higher in rheumatoid arthritis than in the other two groups (Table LVIII). The relative numbers

of/

Table XLVIII.

Age-incidences of Lymphorrhages in Peripheral Nerves in Rheumatoid Arthritis.

Age	Total Cases	Positive Cases	
		No.	Per cent
30 - 39	2	1	50
40 - 49	2	2	100
50 - 59	2	2	100
60 - 69	3	3	100
70 - 79	8	5	62
80 - 89	3	1	33
Total	20	14	70

Table XLIX.

Relationship between Activity of the Disease and the Incidence of Lymphorrhages in Peripheral Nerves in Rheumatoid Arthritis.

	Total Cases	Positive Cases	
		No.	Per cent
Active Rheumatoid Arthritis	8	5	62
Quiescent or Inactive Rheumatoid Arthritis	10	7	70
Total	18	12	67

Table L.

Relationship between the Stage of the Disease and the Incidence of Lymphorrhages in Peripheral Nerves in Rheumatoid Arthritis.

Stage	Total Cases	Positive Cases	
		No.	Per cent
I	0		
II	2	2	100
III	8	6	75
IV	6	4	67
Total	16	12	75

Table LI.

Incidences of Lymphorrhages in Peripheral Nerves in Other Rheumatic Diseases.

Diagnosis	Total Cases	Positive Cases	
		No.	Per cent
Ankylosing spondylitis	1	0	0
Osteoarthritis	1	1	100
Gout	1	0	0
* Rheumatic fever	9	2	22
Systemic lupus erythematosus	3	2	67
Polyarteritis nodosa	6	4	67
Total	21	9	43

* = includes one case of subacute bacterial endocarditis (negative).

Table LII.

Age-incidences of Lymphorrhages in Peripheral Nerves in Other Rheumatic Diseases.

Age	Total Cases	Positive Cases	
		No.	Per cent
10 - 19	1	0	0
20 - 29	3	0	0
30 - 39	3	2	67
40 - 49	5	3	60
50 - 59	3	3	100
60 - 69	4	1	25
70 - 79	1	0	0
Total	20	9	45

Table LIII.

Age-incidences of Lymphorrhages in Peripheral Nerves in Non-rheumatic Diseases.

Age	Total Cases	Positive Cases	
		No.	Per cent
10 - 19	2	0	0
20 - 29	4	0	0
30 - 39	8	2	25
40 - 49	20	4	20
50 - 59	21	3	14
60 - 69	40	6	15
70 - 79	20	2	10
80 - 89	3	1	33
Total	118	18	15

Table LIV.

Alphabetical List of Diseases in which Lymphorrhages were found in Peripheral Nerves.

? Allergic lesions in spleen and lymph nodes
Amyloidosis
Aneurysm of aorta, non-syphilitic
Atheroma, cerebral and coronary
Atheroma of leg vessels

Bronchiectasis

Carcinoids of ileum
Carcinoma, primary site in breast, bronchus, duodenum, gall bladder, kidney, stomach
Cholecystitis
Cirrhosis of liver
Cystitis

Disseminated lupus erythematosus
Duodenal ulcer

Gold, toxic reaction to

Hepatitis, viral
Hernia, strangulated femoral

Infarcts, thalamic

Myasthenia gravis, without thymoma

Nephrosclerosis, benign

Osteoarthritis

Parkinsonism
Pericarditis, acute fibrinous
Peritonitis
Pneumonia, bronchopneumonia
Pneumonia, lobar
Polyarteritis nodosa
Psoriasis
Pyelonephritis or pyelitis

Rheumatic fever, healed, with mitral stenosis
Rheumatoid arthritis

Senile hyperplasia of prostate
Septicaemia, streptococcal

Thromboangiitis obliterans
Trauma, fractured femur with death within a week

Fractured/

fractured skull with transverse myelitis
Tuberculosis, apical
healed apical
chronic pulmonary with tuberculous bronchopneumonia, ileitis and colitis.

Table LV.

Relationship between some General Disease Processes and the Incidence of Lymphorrhages in Peripheral Nerves in Non-rheumatic Diseases.

Disease Process	Total Cases	Positive Cases	
		No.	Per cent
*Inflammation	11	2	18
*General Ischaemia	14	1	7
Renal Failure	2	0	0
Tumours	8	0	0
±Trauma	3	0	0

* See footnote to Table XXXVII, p.

Table LVI.

Size of Largest Lymphorrhages in Peripheral Nerves.

	Total Cases	Logarithm of Size of largest Focus in micra^2.					
		3.0 to 3.9		4.0 to 4.9		5.0 plus	
		No.	%	No.	%	No.	%
Rheumatoid Arthritis	13	2	15	8	61	3	23
Other Rheumatic Diseases	7	2	29	4	57	1	14
Non-rheumatic Diseases	16	6	37	8	50	2	12
Total	36	10	28	20	56	6	17

Table LVII.

Histological Distribution of Lymphorrhages in Peripheral Nerves.

	Total Foci	Histological Site of Foci					
		Endoneural		Perineural		Epineural	
		No.	%	No.	%	No.	%
Rheumatoid Arthritis	222	4	2	68	31	150	68
Other Rheumatic Diseases	95	2	2	51	54	42	44
Non-rheumatic Diseases	97	6	6	28	30	63	65
Total	414	12	3	147	36	255	62

Table LVIII.

Number of Lymphorrhages per Unit Piece of Nerve.

	Total Cases	Number of Foci per Unit Piece of Nerve							
		Nil		0.1 to 0.9		1 to 5		More than 5	
		No.	%	No.	%	No.	%	No.	%
Rheumatoid Arthritis	19	9	46	2	11	4	21	4	21
Other Rheumatic Diseases	19	10	53	4	21	4	21	1	5
Non-rheumatic Diseases	113	96	85	8	7	7	6	2	2
Total	151	115	76	14	9	15	10	7	5

of blocks containing foci is shown in Table LIX.

Comparative Incidence of Lymphorrhages in Muscles and Nerves.

In nearly half of the cases both muscles and nerves were available for study and the comparative incidences of lymphorrhages in the two tissues is shown in Table LX.

Other Focal Lesions.

The reasons for placing foci in this group were the same as in the skeletal muscles, namely, atypical cytology, (Fig. 192) loose or diffuse infiltration (Fig. 193), arteritis (Figs. 194-202) and presence of pigment (Fig. 202). Hypertensive thickening of vessels (Fig. 203) was readily distinguishable from active or healed arteritis and is not considered further. The incidences of these other focal lesions are given in Tables LXI and LXII.

DISCUSSION.

This study of peripheral nerves from 161 cases has failed to reveal any focal lesions specific to rheumatoid arthritis. The lesions found in that disease - lymphorrhages, minor variations therefrom and subacute or chronic arteritis - were all seen in other conditions. Lymphorrhages were found in over thirty other conditions, including such non-rheumatic diseases as bronchiectasis, tuberculosis and malignant tumours. These findings are at variance with those of Freund et al (1942) and/

Table LIX.

Number of Blocks of Peripheral Nerves containing Lymphorrhages.

	Total Blocks	Positive Blocks	
		No.	Per cent
Rheumatoid Arthritis	153	50	33
Other rheumatic Diseases	133	22	17
Non-rheumatic Diseases	646	44	7
Total	932	116	12

Table LX.

Comparative Incidences of Lymphorrhages in Muscle and Nerve.

Diagnosis	Total Cases	Muscle Pos. Nerve Pos.		Muscle Pos. Nerve Neg.		Muscle Neg. Nerve Pos.		Muscle Neg. Nerve Neg.	
		No.	%	No.	%	No.	%	No.	%
Rheumatoid Arthritis	19	11	55	3	16	2	10	3	16
Other Rheumatic Diseases	10	4	40	1	10	1	10	4	40
Non-rheumatic Diseases	31	4	13	4	13	5	15	18	58
Total	60	19	32	8	13	8	13	18	42

Peripheral Nerve in Systemic Lupus Erythematosus.

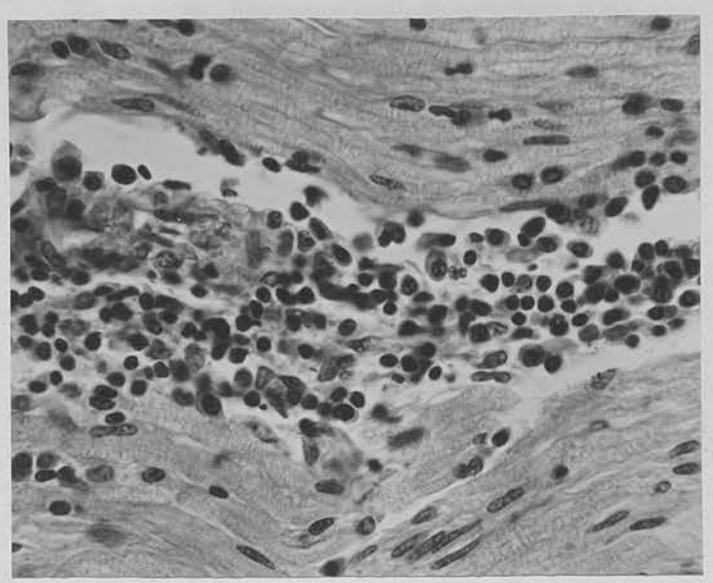

Fig. 192. Case 523 x 450. Femoral nerve. An endoneural focus with an unusually high proportion of plasma cells. See also Fig. 202, p. 294. The patient also had streptococcal septicaemia.

Peripheral Nerve in Polyarteritis Nodosa.

Fig. 193. Case 550 x 100. Femoral nerve. Loose perineural infiltration with lymphocytes. See also Fig. 201, p. 293. The patient also had hypertension and early cirrhosis of the liver.

Peripheral Nerve in Rheumatoid Arthritis.

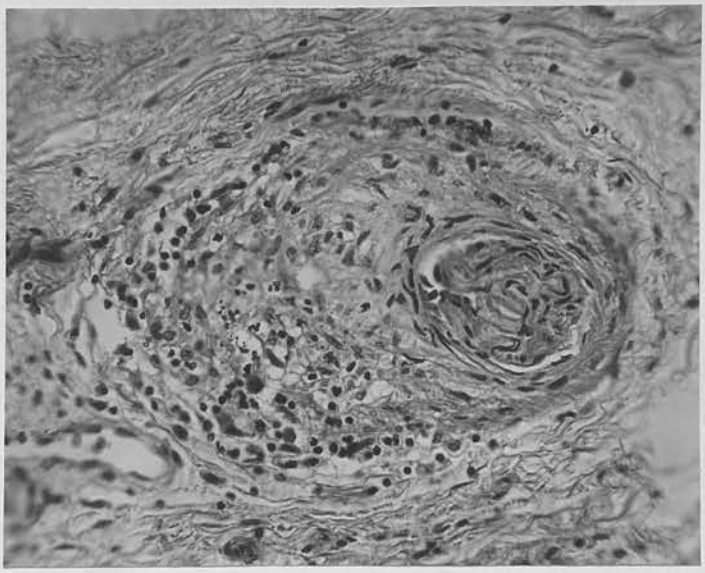

Fig. 194. Case 2 x 250. Sciatic nerve.
An epineural artery showing healing arteritis and organising thrombus.

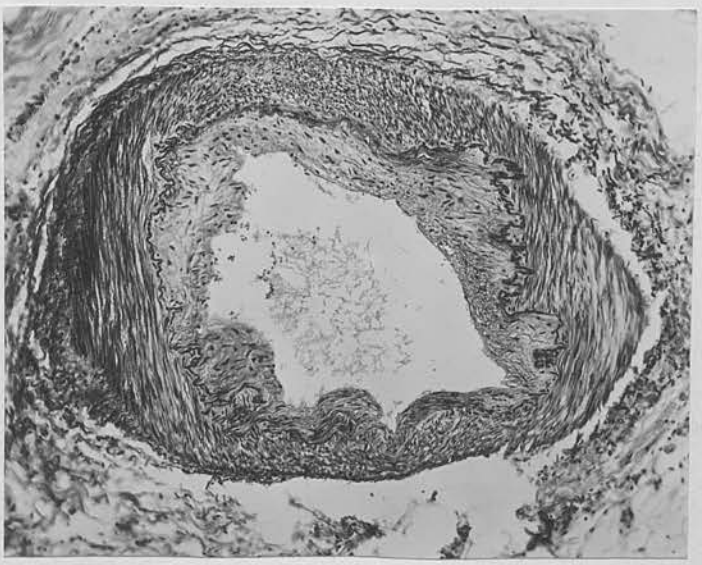

Fig. 195. Case 13 x 50. Another section of femoral nerve. Intimal fibrosis of an epineural artery. The patient was not hypertensive but had healed coronary arteritis (See Figs. 219 and 220, p. 334).

Peripheral Nerve in Rheumatoid Arthritis.

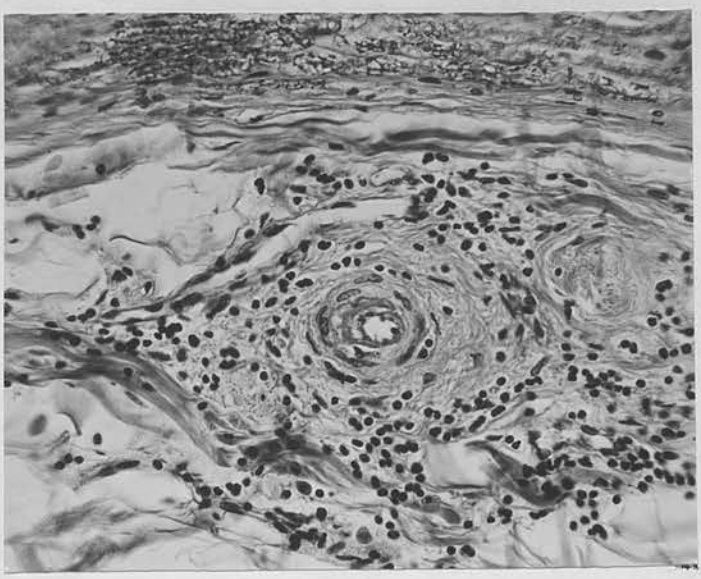

Fig. 196. Case 12 x 250. Brachial plexus. Low-grade arteriolitis in a perineural vessel. This patient had benign hypertension.

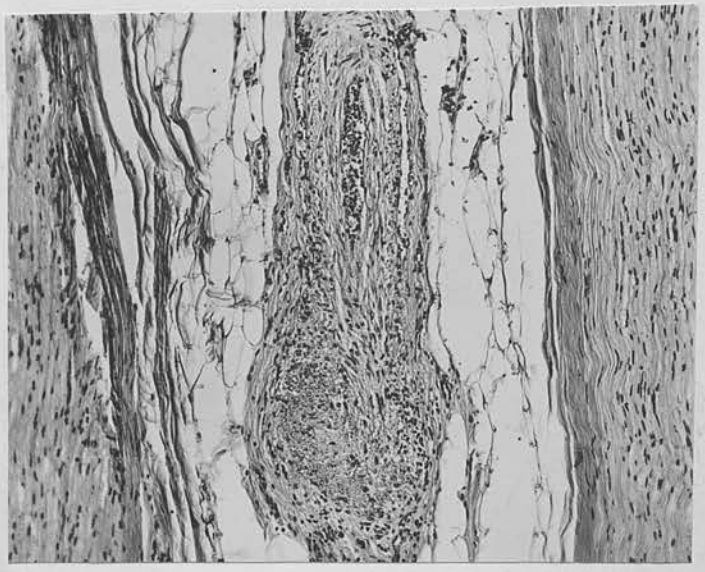

Fig. 197. Case 26 x 100. Femoral nerve. Organising thrombus in perineural vessel with disruption and round cell infiltration of wall (top centre). Small quantities of haemosiderin are present. The patient died of shock following operative reduction of fracture of neck of femur.

Peripheral Nerve in Rheumatoid Arthritis.

Fig. 198. Case 17 x 250. Femoral nerve. Subacute arteritis in epineural tissue. Similar lesions were present in muscle (Figs. 165 and 166, p. 240) and heart (Figs. 222-225, pp. 336 -337). The patient died of acute liver failure following viral hepatitis and had a toxic reaction to gold three weeks before death.

Peripheral Nerve in Thromboangiitis Obliterans.

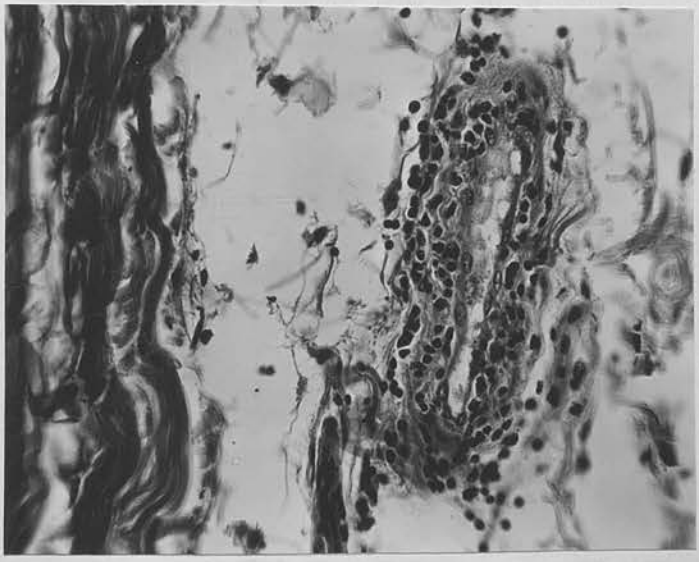

Fig. 199. Case 1284 x 250. Posterior tibial nerve. Endothelial swelling and lymphocytic infiltration of walls of epineural venule.

Peripheral Nerve In Osteoarthritis.

Fig. 200. Case 210 x 250. Posterior tibial nerve. Lymphocytic infiltration and fibroblastic proliferation in walls of epineural venules. The patient also had arteriosclerosis of this limb.

Peripheral Nerve in Polyarteritis Nodosa.

Fig. 201. Case 550 x 100. Femoral nerve. Normal arterial wall (left) becoming completely disrupted with organisation (right centre).

Peripheral Nerve in Systemic Lupus Erythematosus.

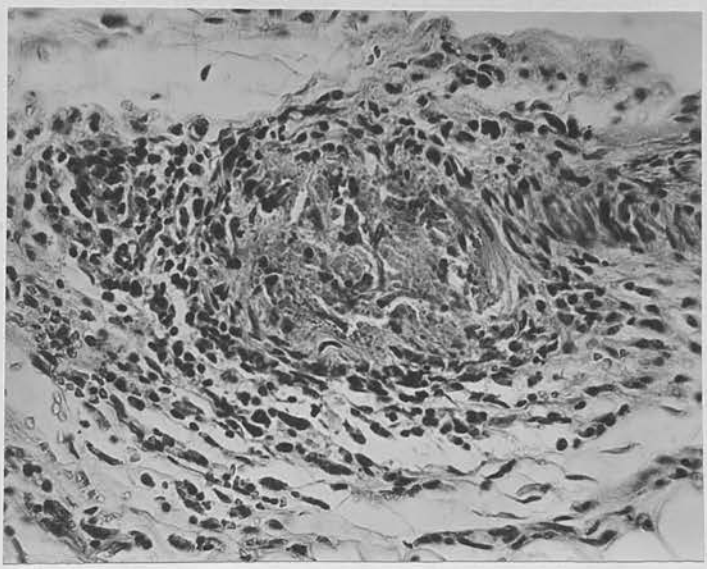

Fig. 202. Case 523 x 250. Femoral nerve. Organising arteritis. Most of the dark, spindle-shaped cells are histiocytes containing haemosiderin.

Peripheral Nerve in Hypertension.

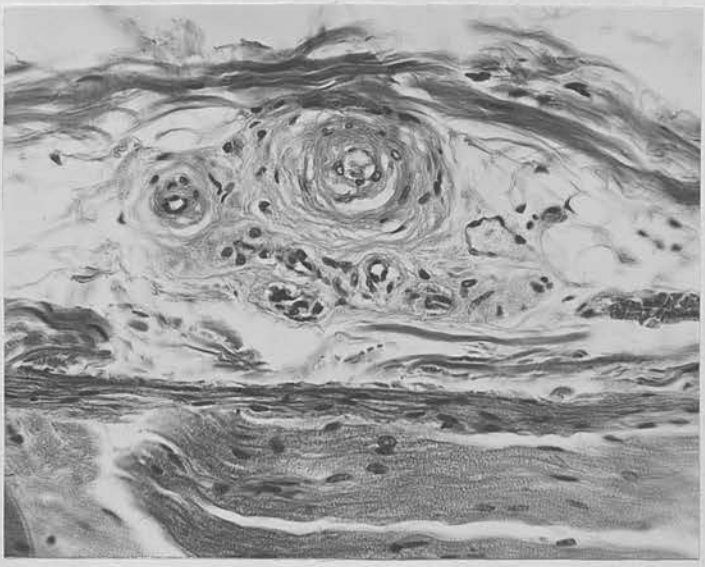

Fig. 203. Case 1500 x 250. Brachial plexus. Reduplication of internal elastic lamina and fibrosis in wall of perineural arteriole.

Table LXI.

Incidences of Other Focal Lesions in Peripheral Nerves

	Total Cases	Positive Cases	
		No.	Per cent
* Rheumatoid Arthritis	20	9	45
Other Rheumatic Diseases	21	9	43
Non-rheumatic Diseases	120	8	7
Total	161	26	16

* Includes the same cases as Tables XLVI (one positive).

Table LXII.

Incidences of Other Focal Lesions in Peripheral Nerves in Other Rheumatic Diseases.

Diagnosis	Total Cases	Positive Cases	
		No.	Per cent
Ankylosing spondylitis	1	1	100
Osteoarthritis	1	1	100
Gout	1	0	0
* Rheumatic fever	9	0	0
Systemic lupus erythematosus	3	2	67
Polyarteritis nodosa	6	5	83
Total	21	9	43

* = includes the same cases as Table LI, p.

and show a close parallel with the results reported above and by other workers (Clawson et al, 1947; Sokoloff et al, 1950) in connection with skeletal muscles.

No definite evidence as to the factors responsible for the occurrence of lymphorrhages emerges from this investigation. However, the study of the comparative incidences of lymphorrhages in muscles and nerves has produced some suggestive evidence. The discrepancy between the incidences in the two tissues is even greater than that shown in Table LX, where it is seen that in 26% of cases only one of the two tissues contained lesions. In four of the 19 cases in which both tissues contained lesions, the number of foci per unit volume of tissue (calculated as indicated on p.225) differed by more than five. This discrepancy is considered to favour the argument, advanced in the preceding section of this thesis, that lymphorrhages are a non-specific reaction to locally produced chemicals rather than a reaction to some local factor.

Lesions were found in the nerves more readily than in the muscles (Compare Tables XLVI, XLVII, LIX and LXI with Tables XXV, XXVI, XLII and XLIV respectively). This was unexpected, for Freund et al (1942) found foci in 16/30, 5/65, 2/42, 10/38 and 18/47 blocks examined in their five cases. In the third case only two nodules were found in the 42 blocks examined. It would appear that/

that many of their blocks were cut in cross section. Because the number of blocks cut in the present study had to be limited, it was decided to obtain the largest area possible by cutting most of the nerves in longitudinal section. This may explain the ease with which lesions were found and their higher incidences in the nerves as compared with the muscles for, in proportion to the total amounts of each tissue in the body, the amount of nerve must have been greater than the amount of muscle examined per case.

In addition to other lesions, arteritis was also more frequently seen in nerves than in muscles, being present in six out of 20 cases compared with two out of 93 cases. The lesions, in both tissues were mostly of a fairly mild, subacute type and the infiltrating cells were lymphocytes, plasma cells and a few histiocytes (Figs. 165, 196 and 198). No evidence of necrosis was seen and this was borne out by the integrity of the internal elastic lamina in those cases where healing or healed lesions were seen (Figs. 166 and 195). This contrasts sharply with the lesions seen in polyarteritis nodosa (Figs. 167 and 201) and systemic lupus erythematosus (Fig. 202) where necrosis was a constant feature. The changes seen here in these diseases correspond very closely with those described many years ago by Wohlwill (1923) in polyarteritis and very recently by Heptinstall and Sowry (1952) in lupus. Lesions very similar

to/

to those seen in muscle and nerve in this series have been described very recently in skeletal muscle in rheumatoid arthritis by Sokoloff et alii (1951). The findings in the present series differ from those of Sokoloff et alii in that thrombosis, which was absent in the six cases studied by them, was present in two of the cases in which nerves were affected (Figs. 194 and 197). It should be noted that, in one of the cases of rheumatoid arthritis studied here (Case 17), subacute arteritis was present in the heart (See p.330) as well as in muscles (Figs. 165 and 166) and nerves (Fig. 198), but in no other organs.

That this series also differs from that of Freund et alii in the relative proportions of perineural and epineural foci arises from the histological criteria used. In this paper, the terms 'epineurium', 'perineurium' and 'endoneurium' are used in accordance with the definitions of Carleton and Leach (1949) and Maximow and Bloom (1948), who limited the term 'perineurium' to the dense, concentric layers of fibrous tissue which surround single fascicles (Fig. 180). Only those foci which impinged upon, or disrupted this layer were classified as 'perineural'. Freund et al. regarded foci which lay "between two sheets of the perineurium " as 'perineural'. One such focus, illustrated in their Fig. 1, would have been classified as 'epineural' in the present series, because it had no contact with the perineurium.

Although/

Although endoneural foci were quite uncommon, the endoneurium was not immune as the American workers suggested. Nor can one agree with them (Steiner et alii) that the perineurium constitutes a barrier between mesodermal and ectodermal tissues, for blood vessels enter and leave the nerve fascicles freely and are frequently accompanied by small numbers of cells, such as lymphocytes, plasma cells and histiocytes, all of which are derived from mesoderm. If one accepts the argument that local factors are an important cause of the lesions, the infrequence of endoneural foci may be explained by the fact that such factors as those listed in TableXXXVIII(See p. 227) were absent in the nerve bundles.

The zonal arrangement upon which Freund and his colleagues laid much stress in the nerves was not seen in this series even when large foci were sectioned serially. This is not surprising, for the conclusions of the American workers were based on five cases. The lesion they described as "characteristic" appears to have been present in all its features in only one of these, whereas in the others, zonal arrangements was imperfect or absent. As in the muscles, most epithelioid cells seen in this study could be identified as capillary endothelium (Fig. 191).

SUMMARY.

1. The literature on focal round cell lesions (lymphorrhages)/

(lymphorrhages) in peripheral nerves has been reviewed. Their existence in porphyria and thromboangiitis obliterans has been known for several years. Recently they have been claimed to be specific to rheumatoid arthritis. Similar lesions, which occur in the skeletal muscles are not specific.

2. The objects of this study were a) to determine whether a focal lesion specific to rheumatoid arthritis occurs in the peripheral nerves, b) to see whether any further light could be thrown on the factors responsible for the occurrence of lymphorrhages and c) to study the comparative incidences of lymphorrhages in skeletal muscles and peripheral nerves.

3. Peripheral nerves have been examined for the presence of focal lesions from 20 cases of rheumatoid arthritis, 21 of other rheumatic diseases and 120 of non-rheumatic diseases. With the exception of a few cases of osteoarthritis and thromboangiitis obliterans, all cases were studied at postmortem, blocks being taken from brachial plexus and femoral nerve. Material from the remaining cases was obtained at amputation.

4. No lesion specific to rheumatoid arthritis was seen. The lesions found in that disease were lymphorrhages, other focal lesions showing minor variations therefrom and subacute or chronic arteritis. These lesions were all found in

other/

other rheumatic diseases. Lymphorrhages were found in over 30 non-rheumatic diseases. The incidence of lymphorrhages was 70% in rheumatoid arthritis, 43% in other rheumatic diseases and 15% in non-rheumatic diseases.

5. The incidence of lymphorrhages in rheumatoid arthritis could not be correlated with age, duration, activity or stage of the disease.

6. The incidence of lymphorrhages and other focal lesions was higher in peripheral nerves than in skeletal muscles, probably because relatively more of the former tissue was examined per case.

SECTION VI.

Cardiac Lesions in Rheumatoid Arthritis.

INTRODUCTION.

The heart in rheumatoid arthritis has been the subject of intensive study during the last decade. On the one hand, pathologists have found lesions of rheumatic heart disease i.e., active, healing or healed rheumatic fever in a much higher proportion of cases than was suspected hitherto, whereas on the other hand clinical examination of patients revealed a much lower incidence of features of rheumatic heart disease. Various interpretations have been given to these findings. A small number of cases of rheumatoid arthritis have shown cardiac lesions quite different from those of rheumatic heart disease and very like the subcutaneous nodules of the former. During the present investigation the opportunity arose of studying the cardiac lesions of a fairly large series of cases of rheumatoid arthritis. The object of this section of the thesis is a) to investigate the discrepancy between the pathological and clinical incidences of rheumatic heart disease in rheumatoid arthritis, and b) to attempt to determine to what extent the cardiac lesions encountered in rheumatoid arthritis are caused by that disease rather than by rheumatic/

rheumatic heart disease. It will be shown that a discrepancy between pathological and clinical findings is not peculiar to rheumatoid arthritis, being encountered in uncomplicated rheumatic heart disease, that the incidence of rheumatic heart disease is higher in rheumatoid arthritis than in unselected autopsies and that rheumatoid arthritis is itself associated with several types of cardiac lesion, some of which may be confused with true rheumatic heart disease.

The earlier literature on the subject was mentioned by Baggenstoss and Rosenberg (1941) and extensively reviewed by Bywaters (1950). Prior to 1941 there were scattered references to the occurrence of rheumatic heart disease, in an inactive or healed stage, in cases of chronic arthritis. The use of such terms as " arthritis deformans ", "chronic infective arthritis", "deforming arthropathy" and others makes it difficult to assess how many of these cases were rheumatoid arthritis. The various types of chronic arthritis are now clearly defined both clinically and pathologically, so that it should be possible to get accurate information about the incidence of cardiac lesions in rheumatoid arthritis. Unfortunately the situation is still confused by the practice in America and some centres elsewhere of regarding ankylosing spondylitis as a variant of rheumatoid arthritis and of discussing the two conditions together in respect of cardiac and/

and other lesions. Reasons why this conception is not acceptable have already been discussed in this thesis (p. 75). In the review of the literature which follows, all cases diagnosed as ankylosing spondylitis ("Marie-Strumpell disease" or "rheumatoid spondylitis") have been excluded.

The results of ten pathological studies published since 1940 are shown in Table LXIII. It should be noted that Young and Schwedel (1944) actually described 38 cases of " rheumatoid arthritis" two of which are stated to have been " Marie-Strumpell disease." In another 23 cases, both spinal and peripheral joints were affected. But involvement of the spine is rare in true rheumatoid arthritis (Copeman, 1948 ; Fletcher, 1951 (d)), so many of these 23 cases were more likely to be ankylosing spondylitis. Accordingly they have all been omitted from the analysis. Those series in which there is no statement about inclusion or exclusion of cases with spinal involvement were all American (Bennett, 1943 ; Clark and Bauer, 1943 ; Fingerman and Andrus, 1943 ; Graef et alii, 1949) so that they possibly included some cases of spondylitis.

The criteria used for diagnosis of rheumatic heart disease varied considerably. Thus Baggenstoss and Rosenberg and Young and Schwedel accepted cases with pericarditis alone as rheumatic, whereas in the other series valve deformities were considered necessary to establish the diagnosis. The incidence of/

Table LXIII.

Incidence of Rheumatic Heart Disease in Cases of Rheumatoid Arthritis coming to Autopsy.

Author	Total Autopsies	Number with Pathology of RHD	% of total	Number with Pathology of RHD but no history of RF or clinical evidence of RHD	% of total
Baggenstoss and Rosenberg (1941)	19	12	63	10	53
Bayles (1943)	17	4	23	4	23
+ Bennett (1943)	48	7	15		
Smyth (1943)	10	5	50		
+ Clark and Bauer (1948)	45	?9	20	7	15
+ Pingerman and Andrus (1943)	61	19	31	17	28
+ Graef, Hickey and Altmann (1949)	66	26	39		
Young and Schwedel (1944)	13	10	77	9	92
Bywaters (1950)	27	5	18	3	11
Jonsson et alii (1952)	65	23	35		
Total	371	120	35	50	21

+ no statement about whether ankylosing spondylitis excluded.

incidence of active rheumatic carditis, in the form of myocardial Aschoff bodies also varied. Baggenstoss and Rosenberg found them in 50% of their cases, whereas Fingerman and Andrus found them in only 5% and Bennett did not see any at all.

The incidence of rheumatic heart disease in rheumatoid arthritis is much higher than that recorded in unselected autopsies, taking into account even the lowest figure in Table LXIII. The incidence of rheumatic heart disease in three large series of unselected autopsies is shown in Table LXIV. When allowance is made for the fact that these results were based largely on reviews of autopsy reports together with the examination of such sections as were available, whereas in the various series of rheumatoid arthritis cases special attention was paid to the heart, the significance of the difference is lessened. More recent studies of the heart in non-rheumatic diseases in which particular attention was paid to " rheumatic" stigmata have recorded a very much higher incidence. Thus Hall and Anderson (1943) found " minimal thickening of the mitral valve " in 66% and microscopic evidence of "positive healed rheumatic infection " in 61% of 112 hearts free of gross valvular deformities. Unfortunately several of their criteria of rheumatic heart disease are not acceptable as such. The incidence of 52% of rheumatic or rheumatic-like lesions in 145 hearts studied by Reifenstein (1947) must also be accepted with reserve for no criteria or illustrations were given.

Table LXIV.

Incidence of Rheumatic Heart Disease in Unselected Autopsies.

Author	Total Cases	Number with Pathology of RHD	% of total
Claiborne and Wolff (1941)	26015	887	5
Clawson (1941)	30265	870	3
Wartmann and Hellerstein (1949)	2000	104	5

It will be noted (Table LXIII) that clinical features of rheumatic heart disease were absent in nearly a third of the cases of rheumatoid arthritis in which the lesions were discovered at autopsy. This is reflected in the incidence of clinical features of rheumatic heart disease in a number of series of living patients reported during the last eighteen years (Table LXV). Some cases of ankylosing spondylitis are probably included in this Table, for three of the reports were American (Dawson and Tyson, 1936 ; Dawson, 1943 ; Bayles, 1943). Some recent clinical reports have not been included in the Table because in them rheumatoid arthritis and ankylosing spondylitis were assessed together in such a way that they could not be separated (Rosenberg et alii, 1950). A higher clinical incidence is recorded by Jonsson et alii (1952) who found abnormalities on clinical, radiological, electrocardiographical or phonocardiographical examination in 32% of 37 cases of rheumatoid arthritis. These workers do not state what proportion of the abnormalities were indicative of rheumatic heart disease.

The occurrence of cardiac lesions in juvenile rheumatoid arthritis was mentioned in the original description of that condition by Still (1897) who found obliteration of the pericardial cavity in all three cases upon which autopsy was performed. In one of these cases the mitral valve was a little thickened. More recently Schlesinger (1949) has noted/

Table LXV.

Clinical Evidence of Rheumatic Heart Disease in Cases of Rheumatoid Arthritis not coming to Autopsy.

Author	Total Cases	Number with Clinical Evidence of RHD	% of total
Master and Jaffe (1934)	50	0	0
Dawson and Tyson (1936)	100	7	7
Colver (1937)	69 (juvenile RA)	0	0
Bayles (1943)	100	5	5
Dawson (1943)	40	14	35
Ellman (1944)	100	8	8
Fraser (1945)	110	15	14
Lucchesi et alii, (1947)	50	0	0
Rogen (1947)	33	1	3
Fischmann and Gwynne (1948)	60	1	2
Horwitz (1948)	70	4	6
Total	782	55	7

noted pericarditis in six out of 20 cases of juvenile rheumatoid arthritis.

In addition to lesions apparently indistinguishable from those of active or healed rheumatic heart disease, changes have been described which were regarded as peculiar to rheumatoid arthritis. These lesions have had a structure very similar to that of the subcutaneous nodules found in the disease and have been described in nine cases (Baggenstoss and Rosenberg, 1944 ; Clark and Bauer, 1948 ; Gruenwald, 1948 ; Graef et alii, 1949 ; Raven et alii, 1949 ; Bywaters, 1950). Baggenstoss and Rosenberg regarded the lesions in their two cases as rheumatic, because " definite " lesions of rheumatic heart disease were also present and the differences between the " rheumatoid " lesions and those of rheumatic heart disease were interpreted as of degree only. Bywaters regarded the granulomatous lesion as peculiar to rheumatoid arthritis. He included two other cases as showing rheumatoid lesions in one of which there was pericarditis only, the cardiac lesion being very similar to those in the synovial tissue in the same case, and in the other there was adhesive pericarditis and non-specific myocarditis. It is doubtful if either of these cases can be accepted as showing lesions specific to rheumatoid arthritis. Graef et alii (1949) found a further lesion in two cases - inflammation of coronary arteries resembling polyarteritis nodosa. They do not state whether a similar arterial lesion was present elsewhere in the body in these cases.

The/

The conclusions drawn from all these studies of the heart in rheumatoid arthritis have varied but can be summarised as :-

a) rheumatoid arthritis and rheumatic fever form a continuous sequence of a single disease process. The differences in clinical features depend largely on age and such other factors as individual susceptibility,

b) that the two are separate diseases and their co-existence coincidental or

c) that some of the " rheumatic " lesions are caused not by rheumatic fever but by the agent(s) responsible for rheumatoid arthritis. The nodule-like lesions are to be included in this group.

MATERIAL AND METHOD.

The heart has been studied in 61 cases of rheumatoid arthritis. This included 21 males and 40 females whose ages ranged from $2\frac{1}{2}$ to 83 years (average 59.9 years). The duration of the arthritis was known in 44 cases and ranged from 3 months to 33 years (average 8.6 years). The series included 23 cases admitted for treatment of the rheumatoid arthritis itself and 38 admitted for treatment of intercurrent diseases (including toxic reactions to gold used in treatment of the arthritis). Death occurred after periods of observation ranging from a few hours to several years, so that clinical examination/

examination of the heart varied considerably, particularly in those admitted for treatment of intercurrent diseases.

In 37 cases, the heart was available for detailed study. Macroscopic examination included cutting through the valve rings at intervals of 2-3mm. and careful inspection of the sections obtained. Six blocks were taken in each case from the standard sites defined by Gross et alii (1930) and in most of them additional blocks were taken. In the other 24 cases, information about the lesions in the heart was obtained from the clinical notes and autopsy reports, supplemented by study of a single section from the interventricular septum in 19 of them.

The lesions in the heart in rheumatoid arthritis were compared with those in 267 cases of rheumatic heart disease in the absence of rheumatoid arthritis. These cases included 49 of active rheumatic carditis, 6 of active rheumatic carditis plus subacute bacterial endocarditis, 195 of healing or healed rheumatic carditis and 17 of healed rheumatic carditis plus bacterial endocarditis. Because of the doubt as to the cause of calcified stenosis confined to the aortic valve (Clawson et alii, 1936 ; Schval and Gross, 1936 ; Karsner and Poletsky, 1947 ; Hultgren, 1948) cases in which this was the only lesion have been excluded. Clinical notes, when available, were examined in all cases where rheumatic heart disease was discovered

at autopsy but was not mentioned in the clinical abstract supplied to the pathologist. Histological material, varying from multiple to single blocks from 134 cases were studied including all the cases of uncomplicated active rheumatic carditis. In all of these cases there was a block from the posterior cusp of the mitral valve with adjacent auricle and ventricle.

The pathological lesions regarded as evidence of rheumatic heart disease were Aschoff bodies of the types described by Gross and Ehrlich (1934 (a)), active or healed valvulitis (Gross and Friedberg, 1936 (a and b) ; Gross, 1937) unless other causes were found (bacterial endocarditis, syphilis), and active or healed endocarditis of the posterior wall of the left auricle (MacCallum, 1925 ; von Glahn, 1926 ; Sohval and Gross, 1936). Lesions which were regarded as compatible with rheumatic heart disease, were active or healed pericarditis, diffuse or focal myocarditis, mural endocarditis in situations other than the posterior wall of the left auricle and active or healed arteritis of the types described by von Glahn and Pappenheimer (1926), Gross et alii (1934, 1935) and Karsner and Bayless (1934). Changes in valves (Gross and Kugel, 1931) and vessels (Gross et alii, 1934) due to age were taken into account in assessing the significance of the changes found. When there was any doubt as to whether or not a focal lesion was an Aschoff body, it was regarded as non-specific (Gross, 1929). The criteria regarded as/

as indicative of active rheumatic heart disease were Aschoff bodies and recent verrucous valvulitis.

RESULTS.

Lesions which fulfilled the criteria regarded as indicating rheumatic heart disease were found in 10 out of the 61 cases of rheumatic arthritis, an incidence of 16 per cent. These cases will be considered in groups according to the presence or absence of a history of rheumatic fever or of clinical features of rheumatic heart disease. In a further eight cases, lesions compatible with rheumatic heart disease were present in the absence of any clinical abnormalities (Table LXVI).

Cases with a previous history of rheumatic fever. (Table LXVII).

Both cases are abstracted in full in the appendix (p.391 & 403). It should be noted that clinical features of rheumatic heart disease were present in only one of them (Case 14) although both showed mitral stenosis which was slight in Case 14 and more marked in Case 19 (Fig. 204). The valvulitis in Case 14 was unexpectedly active (Fig. 205) and widespread, features which were seen in two other cases (Cases 81 and 192). In Case 19 the valvular lesion resembled more closely that of inactive rheumatic valvulitis (Fig. 206). Both cases showed evidence of previous damage to small arteries in the left ventricular myocardium (Figs.

Table LXVI.

Incidence of Rheumatic Heart Disease in Present Series.

Pathological features of RHD present :-	
Previous history of rheumatic fever	2
No history of rheumatic fever, but clinical features of RHD present	5
No history of rheumatic fever or clinical features of RHD	3
	10
Lesions suggestive of RHD present	8
No lesions of RHD present	43
	61

Table LXVII.

Lesions of Rheumatic Heart Disease in Cases of Rheumatoid Arthritis with a previous History of Rheumatic Fever.

Case No.	Sex	Age	Rheumatoid Arthritis		Rheumatic Fever	Clinical Features of Rheumatic Heart Disease.	Pathological Lesions	
			Duration (yrs)	Clinical Activity at Death			Macroscopic	Microscopic
14	F	82	6	Inactive	In childhood	None	Pericardial fibrosis Nodular fibrosis MV: Short, thick chordae Marked coronary atheroma	Fibrosis and calcification (MV) with diffuse chronic inflammation. Healed arteritis and perivascular fibrosis L.V.
*19	M	56	10	Active	32 to 36 years previously	Double mitral murmur	Pericardial fibrosis Fibrosis MV : Short, thick chordae Fibrosis AV Coronary atheroma	Healing valvulitis with calcification MV Perivascular fibrosis LV

Key to Tables

Pathological Lesions -

TV = tricuspid valve MV = mitral valve AV = aortic valve RA = right auricle.
RV = right ventricle L+ = left auricle LV = left ventricle
+ = only one or two sections examined.

* = Case of " Felty's " Syndrome.

Heart in Rheumatoid Arthritis.

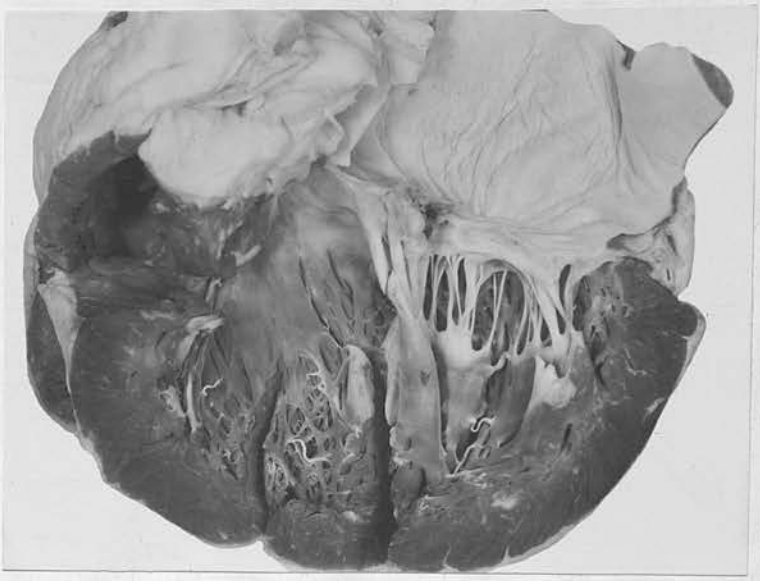

Fig. 204. Case 19. Mitral valve and ventricles. The mitral cusps are grossly thickened and fused at the commissures. There is patchy calcification with superficial ulceration at the right commissure. Chordae are short and thick. Focal scarring of the left ventricular myocardium and hypertrophy of the right ventricle (left) are seen. See also Figs. 206, p. 219 ; Fig. 208, p. 320.

Heart in Rheumatoid Arthritis.

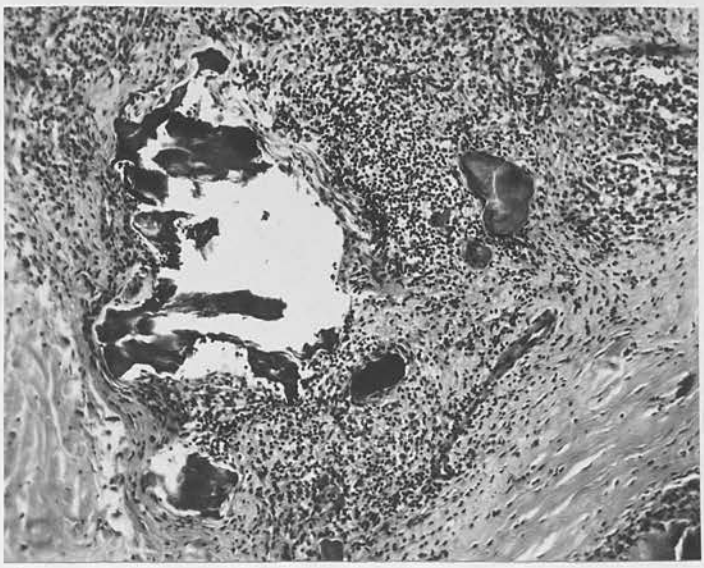

Fig. 205. Case 14 x 100. Posterior cusp of mitral valve. Plaques of calcium surrounded by diffuse chronic inflammation and an outer zone of dense fibrous tissue. See also Fig. 207, p. 320.

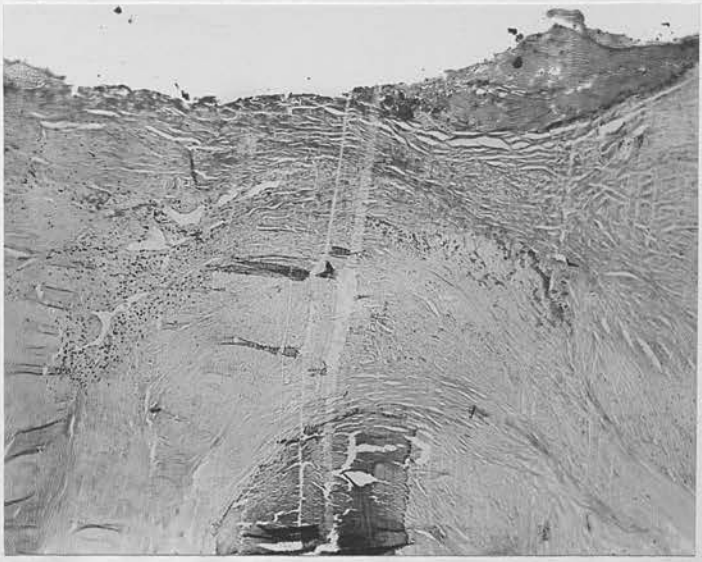

Fig. 206. Case 19 x 50. Posterior cusp of mitral valve. Old vegetation (top right), abnormal vascularity and round cells (centre left) and calcification (bottom).

Heart in Rheumatoid Arthritis.

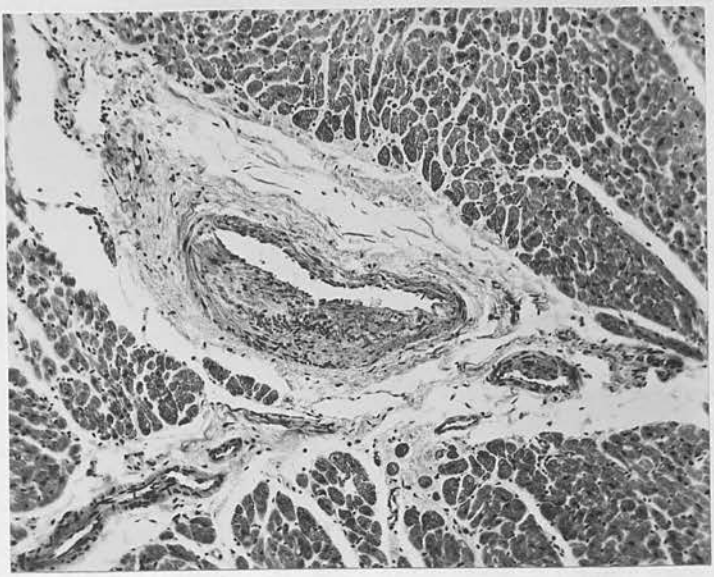

Fig. 207. Case 14 x 100. Posterior papillary muscle. Excentric intimal fibrosis and distortion of elastic tissue. Well marked atheroma present in main coronary arteries.

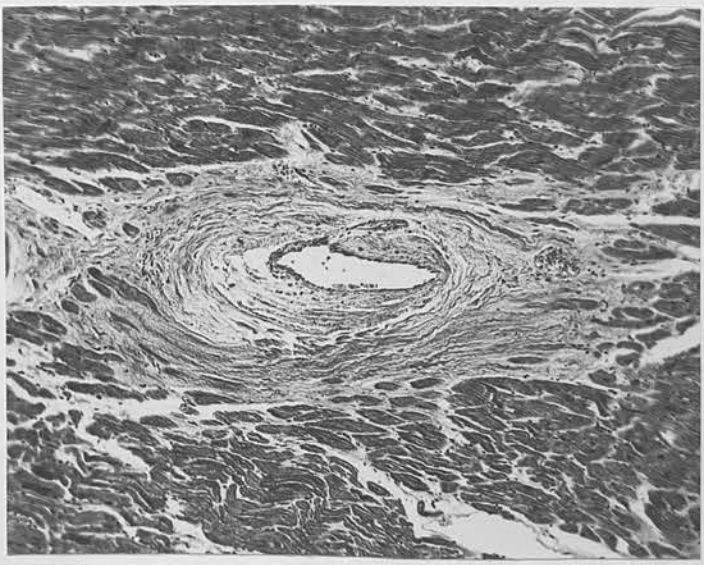

Fig. 208. Case 19 x 100. Right ventricle. Healed arteritis and periarterial fibrosis. Minimal atheroma present in main coronary arteries.

207 and 208).

Cases with no previous history of rheumatic fever, but clinical features of rheumatic heart disease (Table LXVIII).

Two of these cases are abstracted in full in the Appendix (Cases 25 and 26, p. 409 & 414). Clinical features of rheumatic heart disease were present in them all and all showed naked eye lesions indicative of the disease. Case 25 is the only one in which recent vegetations (Figs. 209-211), Aschoff bodies (Fig. 212) and acute valvulitis (Fig. 213) were seen. Subacute arteritis was also present (Fig. 214). The degree of mitral stenosis in Case 26 was slight : calcification was of limited extent but was accompanied by fibrosis with vascularisation.

Case 81 was under observation in hospital for 2½ years before death. The disease involved most joints of the limbs causing gross deformities with fibrous ankylosis of the knees. Many subcutaneous nodules were present when the patient was admitted and were excised from two sites for histological examination shortly after admission (See Figs. 88-95, pp. 131-134). No nodules were present at autopsy. The lesions in the mitral valve were similar to those illustrated in Fig. 205 (p. 319) and the vascular lesions to those in Fig. 207 (p. 320) Apart from the features of old-standing inactive rheumatoid arthritis and the cardiac lesions, the pathological lesions found at autopsy were localised tuberculous foci in the lower lobe of the left lung and/

Table LXVIII.

Lesions of Rheumatic Heart Disease in Cases of Rheumatoid Arthritis with no History of Rheumatic Fever but Clinical Features of Rheumatic Heart Disease.

Case No.	Sex	Age	Rheumatoid Arthritis		Clinical Features of Rheumatic Heart Disease	Pathological Lesions	
			Duration (yrs).	Clinical Activity at Death		Macroscopic	Microscopic
25	M	48	1½	Inactive	Double mitral murmur	Adherent pericardium Recent rheumatic vegetations TV, MV, AV. Fibrosis MV and AV	Aschoff bodies and diffuse myocarditis all chambers. Subacute arteritis L Perivascular fibrosi all chambers Subacute valvulitis all chambers
26	F	82	?	Inactive	Double aortic & systolic mitral murmurs. Waterhammer pulse Auricular fibrillation	Nodular calcification MV : short, thick, chordae Fibrosis AV Coronary atheroma	As for macroscopic
81	F	82	5	Inactive	Double mitral and diastolic aortic murmurs	Adherent pericardium Stenosis and calcification MV Fibrosis and calcification AV Coronary atheroma	Chronic endocarditis Healed arteritis and perivascular fibros LV.
175	F	39	8	?	Double mitral murmur	Pericardial fibrosis Stenosis MV : short, thick chordae Healed endocarditis LA	+ As for macroscopic.
187	F	83	?	? Inactive	Mitral diastolic murmur. Auricular fibrillation.	Fibrosis MV	No sections availabl

Key - See Table LXVII, p. 317.

Heart in Rheumatoid Arthritis.

Fig. 209. Case 25. Tricuspid Valve.
Tiny warty vegetations (arrows) are present on the auricular surface of the septal cusp at the line of closure. See also Figs. 210 - 214.

Fig. 210. Case 25. Mitral valve.
Recent vegetations on auricular surface of both cusps at the line of closure.

Heart in Rheumatoid Arthritis.

Fig. 211. Case 25. Aortic valve.
Recent vegetations are seen on the ventricular surface of all three cusps.

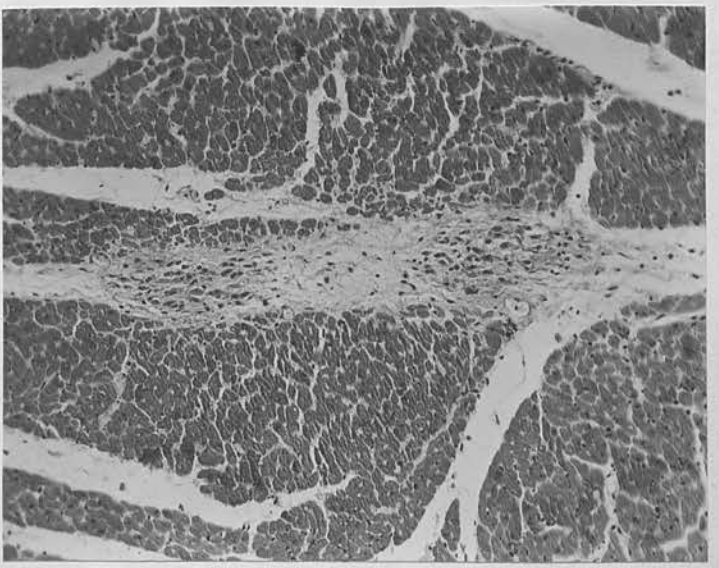

Fig. 212. Case 25 × 100. Interventricular septum. Two fully developed Aschoff bodies lie close together in a small septum.

Fig. 213. Case 25 x 50. Aortic valve. Recent vegetation (top left), necrosis in substance of valve (top right) and subacute valvulitis without Aschoff bodies.

Fig. 214. Case 25 x 100. Posterior papillary muscle. Subacute arteritis with much fibrosis of vessel walls and adjacent tissue.

and confluent bronchopneumonia of the left lung.

Case 175 was in hospital for several months at different times and had shown clinical evidence of severe mitral stenosis throughout the duration of her arthritis. The joints affected were those of the hands and both knees. She was admitted for the last time on the day before death in advanced congestive cardiac failure, the lesions of which were the only ones found apart from the arthritis and cardiac changes. Case 187 had marked deformities of the hands, wrists, knees and ankles but the disease appears to have been quiescent at the time of death. She died from cerebellar haemorrhage following a fall, the other findings being fairly severe benign nephrosclerosis, chronic bronchitis and emphysema.

Cases with no history of rheumatic fever nor clinical features of rheumatic heart disease (Table LXIX).

Despite the absence of clinical features, the diagnosis of rheumatic heart disease was made on macroscopic examination of the heart in all three cases. In Case 48, the arthritis involved the joints of the hands, both wrists, elbows and knees and was accompanied by atrophy of the skin. Marked hypertension (systolic pressure over 300 mm. of mercury and diastolic 130) was present during the last 18 months and was accompanied by right bundle branch block and cardiac failure. Although the macroscopic appearances suggested inactive mitral stenosis/

Table LXIX.

Lesions of Rheumatic Heart Disease in Cases of Rheumatoid Arthritis with no History of Rheumatic Fever nor Clinical Features of Rheumatic Heart Disease.

Case No.	Sex	Age	Rheumatoid Arthritis		Pathological Lesions	
			Duration (yrs).	Clinical Activity at Death	Macroscopic	Microscopic
*48	F	72	Many yrs.	Inactive	Pericardial fibrosis Fibrosis and calcification MV Healed endocarditis LA Fibrosis AV. Coronary atheroma	Chronic endocarditis MV and AV Healed arteritis LV
x181	F	26	22	Inactive	Fibrosis MV and AV	+ As for macroscopic
194	F	? (elderly)	Many yrs.	?	Pericardial fibrosis and adhesions Fibrosis MV and AV	Endocardial fibrosis LA Healed arteritis and peivascular fibrosis LV Fibrosis chordae MV Focal pericarditis LV Focal myocarditis RV and LV

Key - See Table LXVII, p. 317.

* = patient had complete right bundle branch block.

x = case of juvenile rheumatoid arthritis.

stenosis with calcification and inactive aortic fibrosis both valves showed intense active chronic inflammation similar to that shown in Fig. 205 (p. 319).

Information about the other two cases is scanty :-

Case 151 had involvement of the hands and feet and died from acute purulent bronchitis and bronchiolitis with early bronchopneumonia. The mitral fibrosis was accompanied by many small vessels, some with thickened walls, the whole appearance being that of healed valvulitis. Case 194 had extensive old-standing deformities. The vascular lesions resembled those illustrated in Fig. 208 (p. 320). The focal myocarditis was entirely non-specific consisting of occasional small collections of lymphocytes and polymorphs without any resemblance to an Aschoff body. The pericardial lesion was similar but contained histiocytes and a few fibroblasts as well.

Cases with no history of rheumatic fever, nor clinical features of rheumatic heart disease, but lesions compatible with rheumatic heart disease. (Table LXX).

Four of these cases are abstracted in full in the Appendix (Case 2, p. 379 ; Case 13, p. 387 ; Case 17, p. 398 ; Case 43, p. 418). Macroscopic abnormalities compatible with rheumatic heart disease and taking the form of active or healed pericarditis were seen in two of these (Cases 2 and 43)./

Table LXX.

Lesions Compatible with Rheumatic Heart Disease in Cases of Rheumatoid Arthritis with no History of Rheumatic Fever nor Clinical Features of Rheumatic Heart Disease.

Case No.	Sex	Age	Rheumatoid Arthritis		Pathological Lesions	
			Duration	Clinical Activity at Death	Macroscopic	Microscopic
2	M	63	10 yrs.	Active	Adherent pericardium Coronary atheroma	Focal and diffuse myocarditis Perivascular fibrosis LV
13	F	32	4 yrs.	Active	Pericardial effusion	Focal myocarditis all chambers Healed arteritis LV Organising infarcts LV
°17	M	54	32 yrs.	Active	Coronary atheroma	Subacute arteritis RA and pericardium
27	F	82	Many yrs.	Inactive	Coronary atheroma Atheroma AV	Healed arteritis LV
28	F	57	21 yrs.	Active	Pericardial fibrosis	Healed arteritis and perivascular fibrosis LV. Endocardial fibrosis LV
35	F	54	8 yrs.	Active	None	+Healed arteritis LV
43	M	$2\frac{1}{2}$	10 mths.	Active	Adherent pericardium Fibrinous pericarditis	Focal subacute myocarditis RV and LV
117	M	71	4 yrs.	Inactive	None	Cellular fibrosis MV Arteritis LV

Key - See Table LXVII, p. 317.

o = patient had very doubtful history of rheumatic fever immediately before onset of rheumatoid arthritis.

43). The pericardial effusion in Case 13 was part of generalised oedema. No macroscopic evidence of valvular disease was seen in this group. The myocarditis in Cases 13 and 43 was quite non-specific, consisting of small collections of lymphocytes, sometimes with a little fibrin (Fig. 215). In Case 2 diffuse subacute myocarditis of the left ventricle (Fig. 216) was accompanied by focal lesions in which fibrin was deposited (Fig. 217) or collagen fibres affected (Fig. 218) but neither of these could be regarded as Aschoff bodies. Arterioles in relation to one of the focal lesions showed swelling and necrosis of their walls (Fig. 217). The arterial lesions in Case 13 were at a healed stage (Figs. 219 and 220) and were accompanied by tiny organising infarcts in the left ventricle (Fig. 221). In Case 17 the vascular lesions were more active and severe, consisting of dense infiltration of all coats with round cells and destruction of the elastic lamina and in places also of the media (Figs. 222-225).

The lesions in the remaining four cases affected mainly the blood vessels. In Case 27, vessels in the posterior papillary muscle showed endarteritis obliterans or disruption of the media with fibrosis. This patient died of cardiac failure following a fractured neck of femur, no other lesions being discovered at autopsy. Similar lesions were seen in Case 28 in which death was due to extensive pulmonary tuberculosis and in Case 35 (Fig./

Heart in Rheumatoid Arthritis.

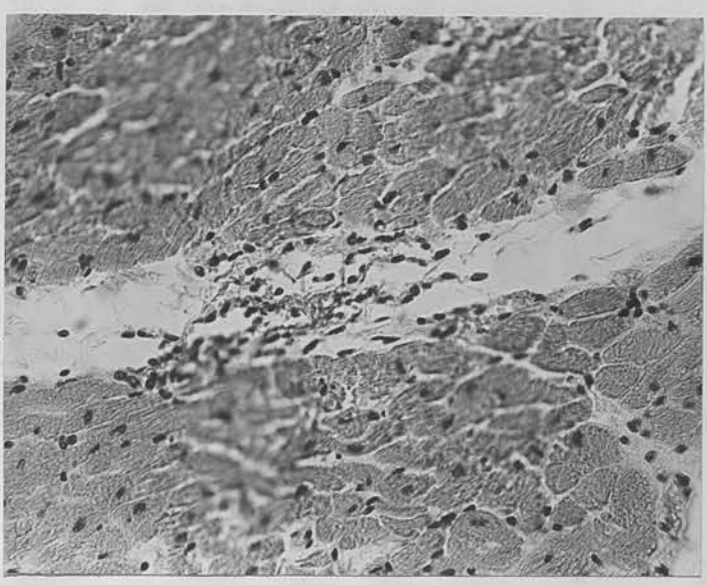

Fig. 215. Case 13 x 250. Left ventricle (near mitral valve). Focal collection of lymphocytes and fibrin in a small septum. See also Figs. 219 and 220, p. 334 ; Fig. 221, p. 335.

Heart in Rheumatoid Arthritis.

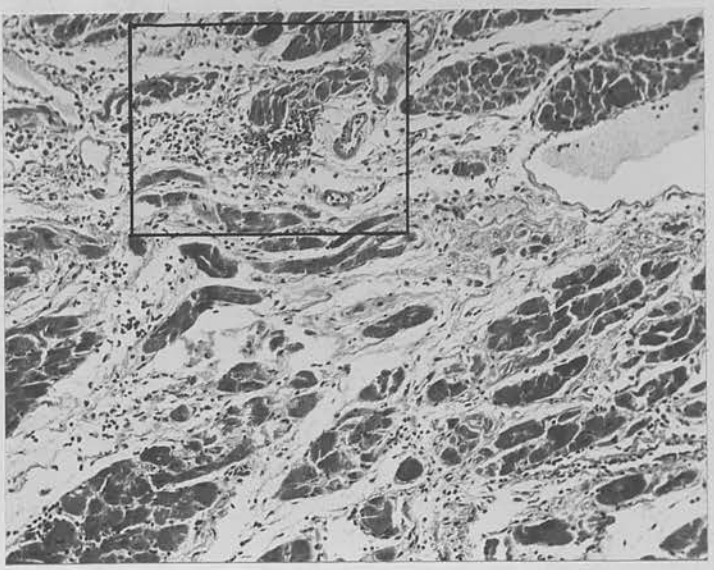

Fig. 216. Case 2 x 100. Left ventricle. Diffuse subacute myocarditis with oedema and focal deposition of fibrin. Necrosis of arteriole (centre top).

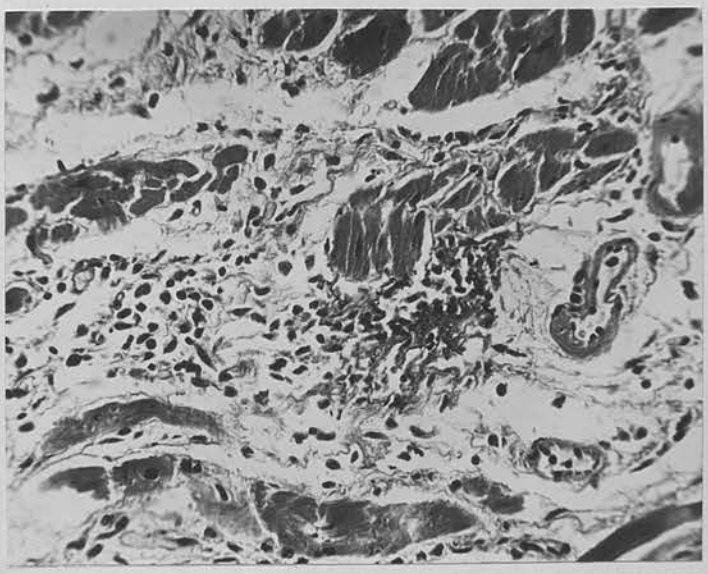

Fig. 217. Case 2 x 250. The field outlined in Fig. 216. Fibrin in a septum surrounded by lymphocytes. This is not an Aschoff body. Necrosis of arteriole (top right).

Heart in Rheumatoid Arthritis.

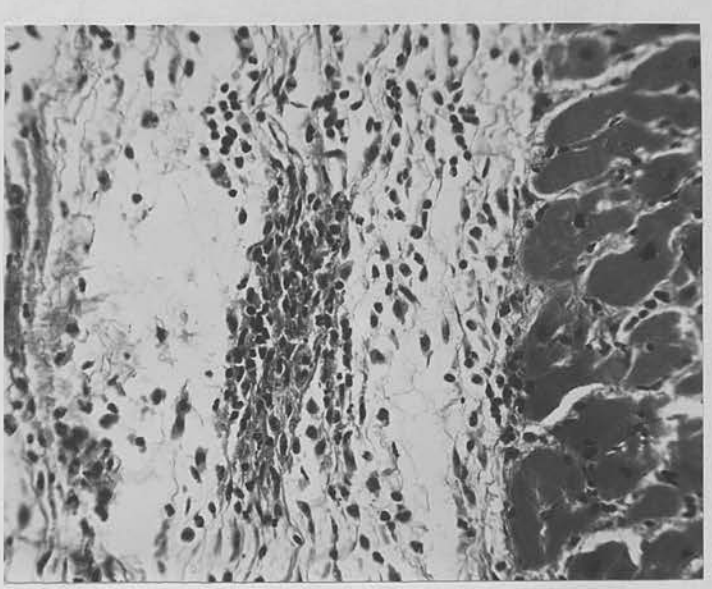

Fig. 218. Case 2 x 250. Left ventricle. Another focus from section shown in Figs. 216 and 217.

Heart in Rheumatoid Arthritis.

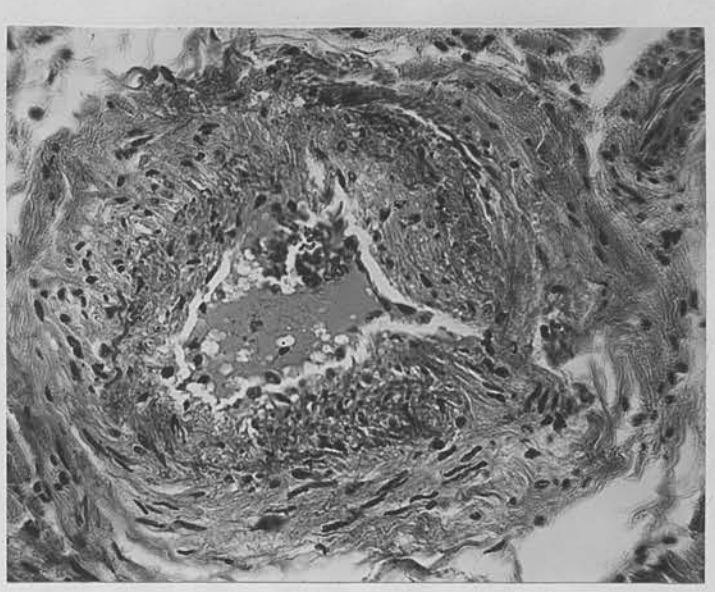

Fig. 219. Case 13 x 250. Posterior papillary muscle. A small artery showing intimal fibrosis, disruption of internal elastic lamina and fibrosis of media. No atheroma in main coronary arteries.

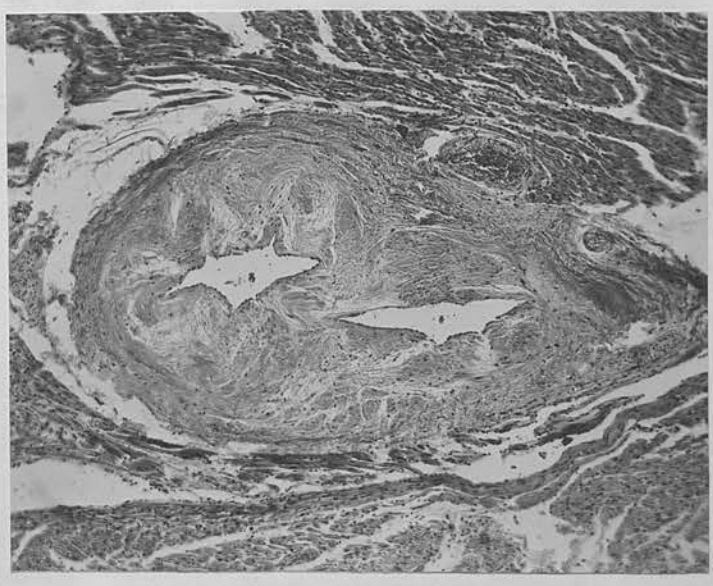

Fig. 220. Case 13 x 50. Another vessel from section in Fig. 219. Old, recanalised thrombosis.

Heart in Rheumatoid Arthritis.

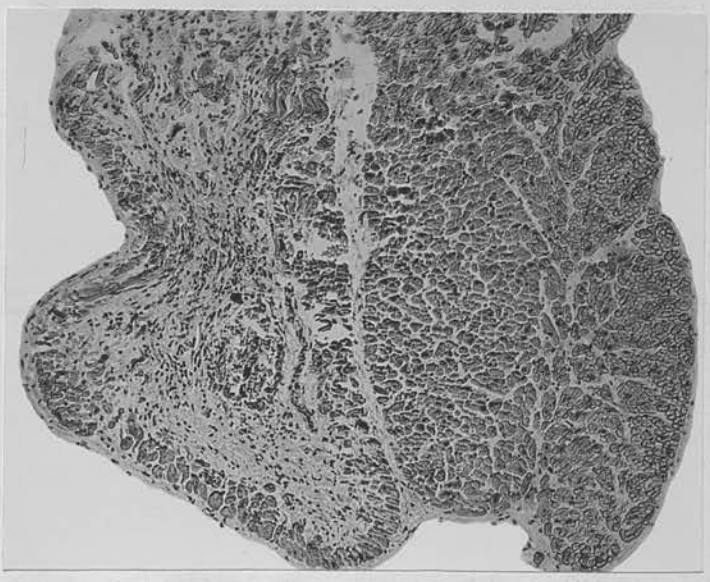

Fig. 221. Case 13. x 100. Interventricular septum. A tiny organising infarct, one of several seen in this section.

Heart in Rheumatoid Arthritis.

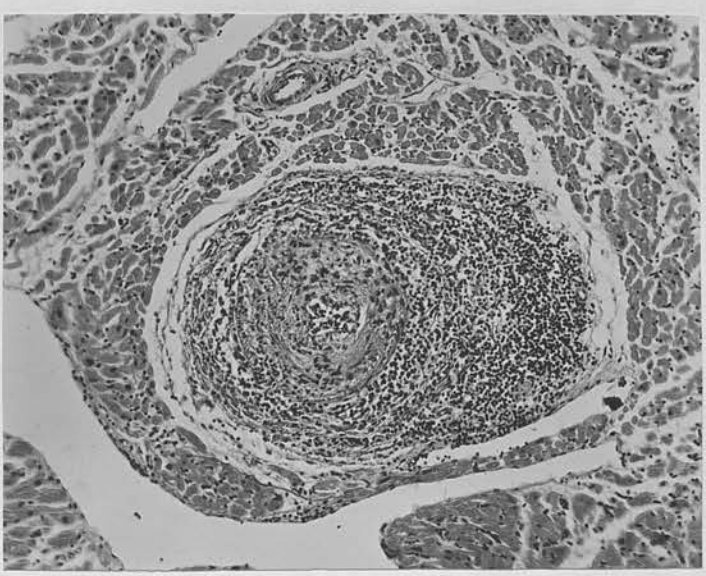

Fig. 222. Case 17 x 100. Right auricle. Intense subacute arteritis with destruction of vessel wall. Similar, but less intense lesions were present in skeletal muscle (Figs. 165 and 166, p. 240) and peripheral nerve (Fig. 198, p. 292).

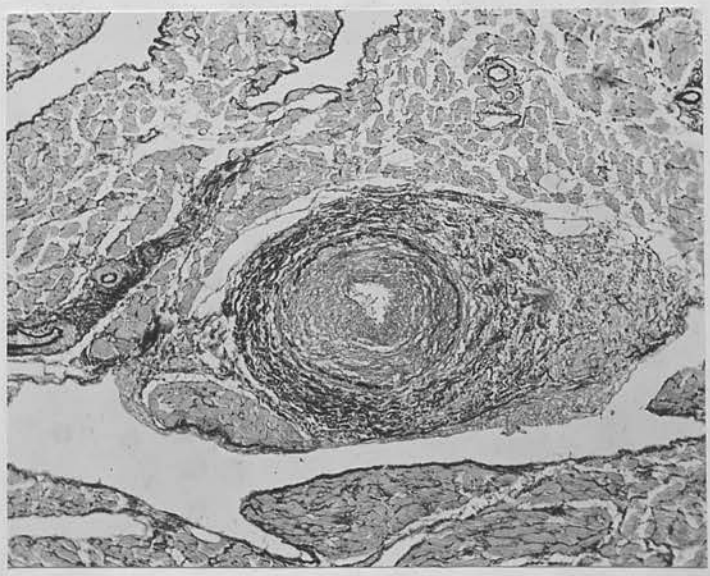

Fig. 223. Case 17 x 100. Another section from same block as Fig. 222 stained by Weigert's elastin method. The elastic tissue is fragmented and displaced.

Heart in Rheumatoid Arthritis.

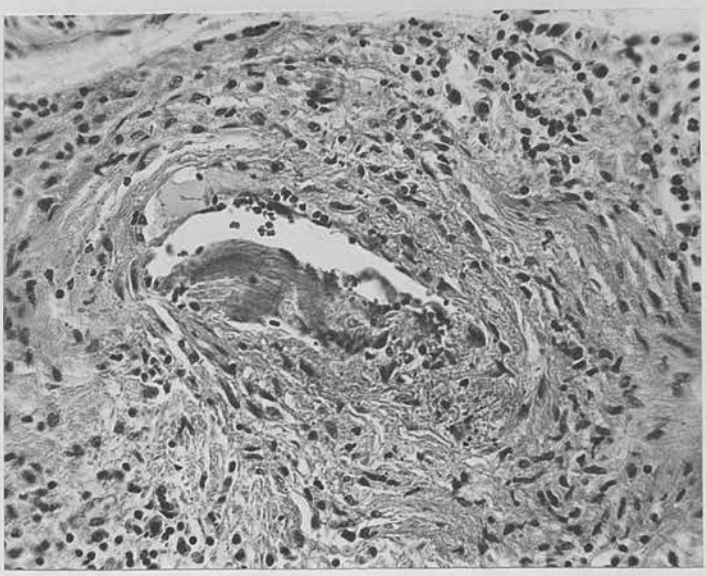

Fig. 224. Case 17 x 250. Epicardium near mitral ring. Partial thrombosis and organising arteritis of a small vessel.

Fig. 225. Case 17 x 100. Another section from the same block as Fig. 224, stained by Weigert's elastin method. Complete destruction of elastic tissue in the vessel shown in Fig. 224 (bottom right). Intimal fibrosis only in others. Marked atheroma present in main coronary arteries.

(Fig. 226) where death was due to pulmonary embolism. The only valvular abnormality encountered in this group was the fibrosis seen in Case 117. This was not accompanied by vessels, vegetations or calcification and only a few lymphocytes were seen (Fig. 227). The vascular lesion in this patient consisted of focal infiltration of histiocytes and lymphocytes in the adventitia of a small artery in the subepicardial fat of the right ventricle (Figs. 228 and 229). Although the wall of the vessel appeared distorted at the site of the lesion, this was due to the origin of a branch and no necrosis had occurred. This patient died of liver failure 40 days after the onset of viral hepatitis, the other lesions found at autopsy being senile hyperplasia of the prostate and carcinoid tumours of the ileum. His arthritis, though extensive, was inactive.

Case with lesions apparently peculiar to rheumatoid arthritis.

One case was encountered (Case 1) in which lesions of the same pattern as the subcutaneous nodules of rheumatoid arthritis were found in the heart. The patient was a woman of 74 with rheumatoid arthritis of 9 years' duration, active during most of its course. During the last few months of life she developed a large fluctuant swelling in the right shoulder region. At autopsy this joint was found to be greatly disorganised with necrosis of adjacent bursae and muscles (See Fig. 52, p. 61). During the last eight months in hospital she went gradually downhill and died of cardiac failure.

There/

Fig. 226. Case 35 x 100. Interventricular septum. Intimal fibrosis, partial loss of internal elastic lamina and disruption of media of a small septal artery.

Fig. 227. Case 117 x 100. Posterior cusp of mitral valve. Cellular fibrosis of whole thickness of cusp with a few lymphocytes near the auricular surface. No vessels, vegetations or calcification were seen.

Heart in Rheumatoid Arthritis.

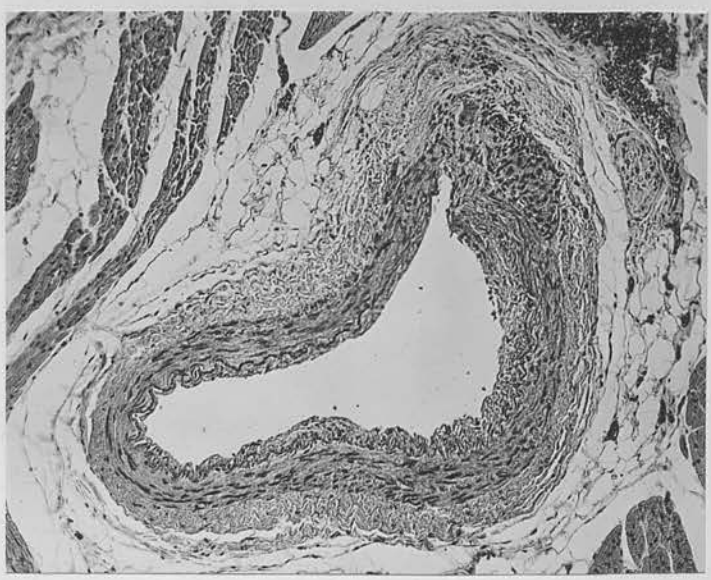

Fig. 228. Case 117 x 100. Right ventricle.
Intimal fibrosis of moderate sized coronary artery with focal lesion in media and adventitia.
Minimal atheroma present in main coronary vessels.

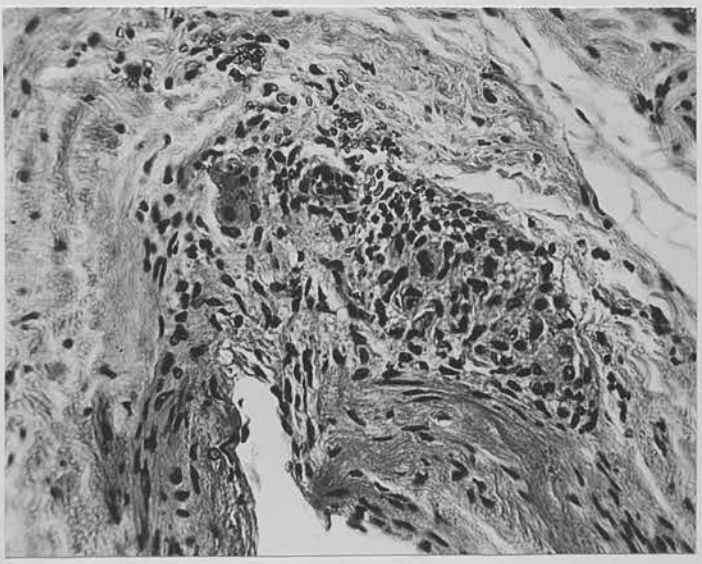

Fig. 229. Case 117 x 250. Focal lesion shown in Fig. 228. Histiocytes and lymphocytes in media and adventitia without destruction of wall. Although media is distorted this is due to the origin of a small branch.

There was no history of rheumatic fever, but the heart was enlarged and a mitral systolic murmur was detected. Macroscopic examination of the heart revealed patchy fibrosis of the epicardium and several foci of necrosis up to 2 mm. in diameter situated in the mitral ring, posterior cusp of mitral valve and its chordae tendineae. These foci were surrounded by narrow zones of firm white tissue. Microscopically (Figs. 230 - 234) the foci had a necrotic centre surrounded by an intermediate zone of cellular fibrous tissue with a radial orientation and containing fibroblasts, histiocytes and undifferentiated mesenchymal cells. Outside this there were densely packed lymphocytes, plasma cells and histiocytes with a variable number of capillaries. In some of the foci, particularly in the valve cusp, myocytes were prominent in the intermediate zone (Fig. 234). In the anterior cusp of the mitral valve there were no foci of necrosis, but diffuse chronic valvulitis with small plaques of calcification and marked thickening of small vessels (Fig. 235). Close to one of the largest foci in the mitral ring, there were two focal collections of large histiocytes rather like those seen in the Aschoff bodies, but the other features of that lesion were not present (Fig. 236). The only other lesions in the heart were occasional tiny loose infiltrations of lymphocytes and plasma cells in septa and early atheroma of large coronary vessels.

DISCUSSION/

Heart in Rheumatoid Arthritis.

Fig. 230. Case 1 x 30. Posterior cusp of mitral valve and ring. Largest of several foci resembling those of rheumatoid subcutaneous nodule. Compare with Fig. 78, p. 122. Diffuse subacute inflammation of adjacent valve tissue and necrosis at valve angle (bottom right).

Fig. 231. Case 1 x 100. Upper left part of focus shown in Fig. 231. Central necrotic zone (right) is surrounded by a zone of fibroblasts arranged radially. Outside this there is dense infiltration with lymphocytes, plasma cells and histiocytes.

Heart in Rheumatoid Arthritis.

Fig. 232. Case 1 x 50. Another field from same section as Fig. 230. Parts of three chordae tendineae are shown. Myxomatous tissue is seen in the upper one and necrosis surrounded by a zone of round cells in the other.

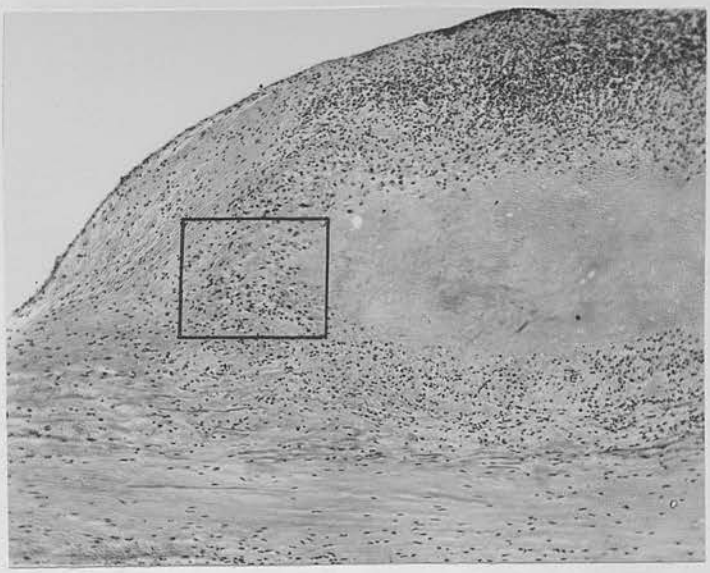

Fig. 233. Case 1 x 50. Another section from posterior mitral cusp. A smaller necrotic focus with intermediate and outer zones partially developed. Note the absence of vegetations in this and the previous figures from this case.

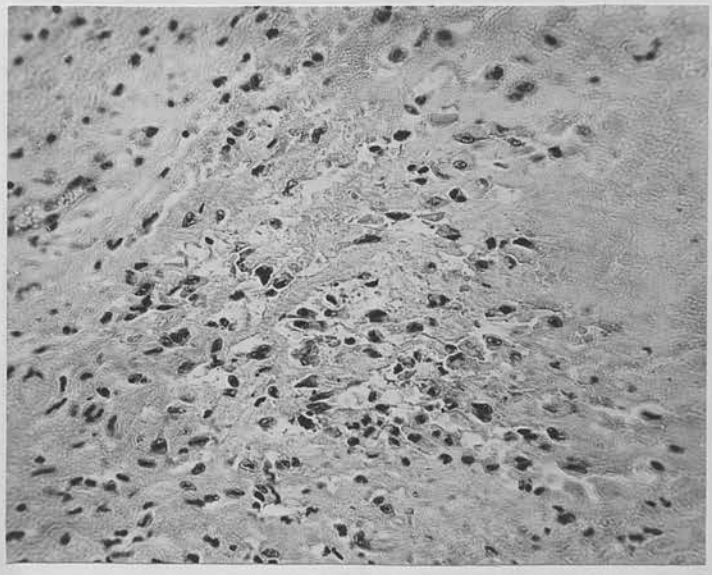

Fig. 234. Case 1 x 250. The field outlined in Fig. 234. Numerous " myocytes " are seen, some of them multinucleate.

Heart in Rheumatoid Arthritis.

Fig. 235. Case 1 x 50. Anterior cusp of mitral valve. Calcification (bottom left) and diffuse chronic valvulitis with marked thickening of two vessels (top right). No necrosis was seen in this cusp. Compare with Fig. 206, p. 319.

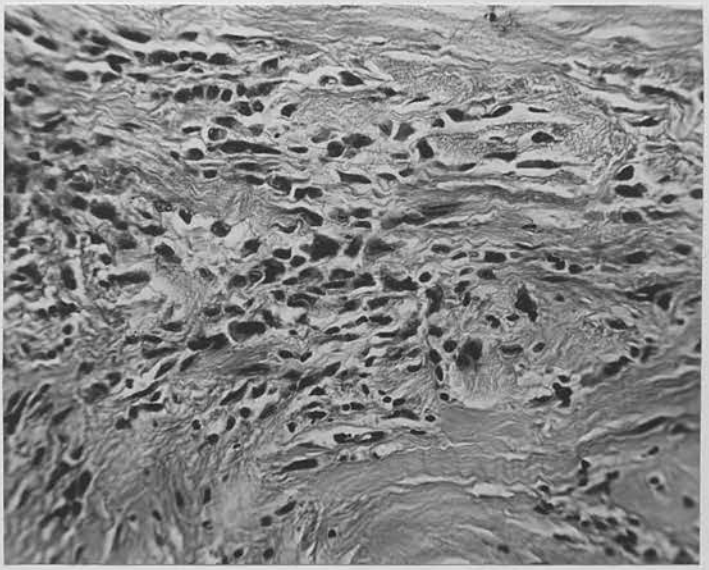

Fig. 236. Case 1 x 250. Another field from same section as Fig. 230. Focal collection of large histiocytes, " myocytes " and a few lymphocytes. Adjacent collagen is swollen and hyaline but not necrotic.

DISCUSSION.

The incidence of pathological features of rheumatic heart disease in this series of 61 fatal cases of rheumatoid arthritis was 16% (10 cases). These lesions were unsuspected clinically in 4 cases (Cases 14, 48, 181 and 194), so that the discrepancy between the pathological and clinical incidence of features of rheumatic heart disease is 40%. This is within the range recorded in previous investigations (Table LXIII, p. 306). Previous writers on cardiac lesions in rheumatoid arthritis have seldom mentioned the fact that clinically unsuspected rheumatic heart disease is discovered at autopsy on patients dying of various diseases other than rheumatoid arthritis. Thus Rogers and Robbins (1947) reviewed 41 cases in which active rheumatic heart disease was diagnosed pathologically. Seven of these cases (average age 55) with valve deformities were not diagnosed as such clinically. Lichtman and Master (1949) observed that clinical examination of the heart was negative in 17% of 176 patients over fifty years of age in whom rheumatic valvular disease was discovered at autopsy. Appel and Kossmann (1951) in a study of 71 patients over 60 years of age found that the diagnosis of mitral stenosis was missed during life in 8 out of 20 cases coming to autopsy. Rosenthal and Feigin (1947) in an article on the pathology of the mitral valve in patients over 40 years of age, commented/

commented that a correct diagnosis of valvular disease is usually made during life up to the sixth decade, but thereafter many patients die undiagnosed. In the control series of rheumatic hearts examined here, valvular lesions were unsuspected during life in 42 out of 214 cases (20%) in which the cardiovascular system was examined clinically before death.

In the light of these recorded observations, the discrepancy between pathological and clinical findings in fatal cases of rheumatoid arthritis looses much of its significance. The average age of the cases in this series showing pathological evidence of rheumatic heart disease was 64.1 years. Furthermore, two of the cases in which mitral stenosis was unaccompanied by clinical features were over 70 years of age (Cases 14 and 48 - aged 82 and 72, respectively). However, there remains to be explained the fact that the incidence of clinical features of rheumatic heart disease in living cases of rheumatoid arthritis (Table LXV) was so much lower than that in fatal cases. These findings were confirmed by the writer for the incidence of clinical features of rheumatic heart disease in 100 consecutive non-fatal cases of rheumatoid arthritis admitted to the Rheumatic Unit, Northern General Hospital was 5% (Table LXXI). Bayles (1943) has observed that the incidences of heart lesions in the published cases of rheumatoid arthritis are higher than the true incidence for the cases studied were/

Table LXXI.

Incidence of Previous Rheumatic Fever or Clinical Evidence of Rheumatic Heart Disease in 100 Consecutive Cases of Rheumatoid Arthritis.

	Total	Clinical eivdence of RHD present	Clinical evidence of RHD absent
Definite history of rheumatic fever	4	2	2
Doubtful history of rheumatic fever	3	2	1
No history of rheumatic fever	93	1	92
	100	5	95

were selected insofar as most of them were admitted to hospital with an unrelated fatal illness. The findings in the present series bear this out for although cases were encountered in which no other lesions were found at autopsy than those of rheumatoid arthritis (e.g., Case 1) all of the cases with rheumatic heart disease died of unrelated diseases.

The incidence of pathological features of rheumatic heart disease in this series (16%) is considerably lower than in most of the published series. This is due partly to sampling errors and to the fact that a limited number of sections was available for study in 19 cases and none at all in another five. The sections from the interventricular septum examined in the 19 cases has been shown to contain vascular lesions not infrequently (Gross et alii, 1935) but it is not the most suitable one in which to look for Aschoff bodies (Gross and Ehrlich, 1934 (b)), nor does it contain any valve tissue. A more important factor influencing the incidence of rheumatic heart disease in rheumatoid arthritis is variation in the criteria used for diagnosis of the cardiac lesions. Only valvular damage, Aschoff bodies and involvement of the left auricular endocardium were accepted as diagnostic in this series. Very similar criteria were adopted by Bayles (1943) and Bennett (1943) who recorded incidences of 23% and 15% respectively in smaller series. Those writers who have recorded higher incidences (See Table LXIII) have all accepted other features such/

such as pericarditis, arteritis and perivascular scars, and diffuse myocarditis as indicative of rheumatic heart disease.

There have been recurrent differences of opinion about the specificity of the lesions found in rheumatic carditis. Since it is proposed to analyse this series to see whether rheumatoid arthritis itself causes a greater variety of cardiac lesions than the nodular ones hitherto associated with it, a brief review of the interpretation of cardiac lesions ascribed to rheumatic fever is relevant.

Despite subsequent reports of the occurrence of " Aschoff bodies " in unrelated diseases (Hall and Anderson, 1943 ; Reifenstein, 1947 ; Valdés - Dapena and Valdés-Dapena, 1951) the writer is in agreement with Kirch (1927) and Saphir (1941, 1942) that the lesions described by these and earlier workers (Fahr, 1921, 1930 ; Rhoads, 1927 ; Siegumnd 1941 ; Masugi et alii, 1937) were not true Aschoff bodies. The variations in structure of the latter have been described in great detail by Gross and Ehrlich (1934 (a)) whose criteria were adopted in this study. Although valve lesions closely resembling those of rheumatic heart disease have been described in systemic lupus erythematosus (Rich, 1946-47) and polyarteritis nodosa (McCall and Pennock , 1944), these diseases are readily distinguishable by the presence of their characteristic lesions. Indeed the valve lesions of/

of lupus and rheumatic fever are usually themselves distinguishable (Gross, 1940). The valve lesions of subacute or acute bacterial endocarditis and of syphilitic endocarditis can also be differentiated by the presence of the other lesions which accompany them. Mural endocarditis occurs in lupus erythematosus (Libman and Sacks, 19 24 ; Gross, 1940) but is of different distribution from that of rheumatic fever (MacCallum, 1925 ; von Glahn, 1926 ;Sohval and Gross,1936). Mural endocarditis in polyarteritis nodosa has been said to be indistinguishable in some cases from that of rheumatic fever (Selzer and Horwitz, 1949) but the presence of characteristic lesions elsewhere will differentiate the two diseases.

Whereas the above-mentioned lesions can be regarded as indicative of rheumatic heart disease, the other lesions which occur in that condition are not specific and can only be regarded as compatible with rheumatic involvement. Thus, the arteritis which was regarded as specific by von Glahn and Pappenheimer (1926), Karsner and Bayless (1934) and Friedberg and Gross (1934) was likened to that of polyarteritis nodosa by Aschoff (1904) in his original description of the lesion named after him. Similar conclusions were reached by many later workers (Geipel, 1907 ; Wohlwill, 1923 ; MacCallum, 1925 ; Klinge and Vaubel, 1931 ; Wild, 1933 ; Collins, 1938(b);Rich and Gregory, 1943 ; McKeown, 1945 ; de Brux, 1948 ; Pagel, 1951). Vascular lesions/

lesions of the same type have been described in systemic lupus erythematosus (Klemperer et alii, 1941 ; Coburn and Moore, 1943 ; Griffith and Vural, 1951), dermatomyositis (Fahr, 1921(b)) and scleroderma (Pollack, 1940). Many of the arterial lesions described by Gross et alii (1935) in cases of rheumatic fever represent the end result of an arteritis and the authors themselves admit that the necrotising arteritis seen was indistinguishable from that of polyarteritis nodosa. It should be noted that this and other papers published prior to 1935 were written at a time when polyarteritis nodosa was much less frequent than it is at present and that cases of this disease of limited anatomical distribution are occasionally encountered. (One case seen in the Royal Infirmary, Edinburgh during the period of this study was confined to the heart). The perivascular scarring usually regarded as indicative of previous rheumatic myocarditis (Aschoff, 1919 ; Klinge, 1931 (b) ; Clawson, 1940) has been described in polyarteritis nodosa (Middleton and McCarter, 1935) and in serum sickness (Clark and Kaplan, 1937). Although adherent pericardium and pericardial fibrosis are frequently regarded as rheumatic, Smith and Willius (1932 (a)) in a study of 73 cases of chronic adherent pericarditis in which the aetiology could be established found that rheumatic fever was the cause of only 31 cases. In similar studies of 62 cases fibrinous pericarditis and " soldier's patches" (pericardial fibrosis), rheumatic carditis was/

was present in only 9 cases (1932 (b)) and in 113 cases of pericarditis with effusion only 8 cases had lesions of rheumatic heart disease (1932 (c)). Diffuse myocarditis and focal myocarditis without Aschoff bodies cannot be regarded as indicative of rheumatic heart disease since they occur in many other conditions (Saphir, 1941, 1942).

There are several findings in the present series which suggest that rheumatoid arthritis itself is a more important cause of cardiac lesions than is generally recognised. Firstly, the average age at death in the cases of arthritis in this series (64.1 years) is considerably higher than in the control cases (47.5 years). The difference is even more striking when only cases with evidence of activity of the cardiac lesions are considered, the figures being 71 years and 34.5 years respectively. Seeondly, of the six cases in this series in which lesions due to other diseases were inadequate to explain death (Cases 1, 2, 8, 9, 175 and 178), three showed cardiac involvement (Cases 1, 2 and 175). The lesions in two of these were not indicative of rheumatic heart disease, consisting of rheumatoid nodular lesions in Case 1 (Figs. 230-236, pp. 342-45) and focal and diffuse myocarditis (Figs. 216-218, pp. 332-333) in Case 2. The findings in Case 1 do not support the contention of Baggenstoss and Rosenberg (1944) that the large nodular lesions are rheumatic in origin for no stigmata of rheumatic heart disease were found. Thirdly the degree of inflammation which

accompanied/

accompanied the apparently inactive mitral stenosis and calcification in Cases 14, 48 and 81 (See Fig. 205, p. 319) is quite unlike that found in uncomplicated rheumatic disease. Furthermore the appearances in the mitral valve in these cases were similar to those in the anterior cusp of that valve in Case 1 which had rheumatoid nodular lesions in the other cusp. Sections of stenotic mitral valves with calcification were available in 31 cases in the control series. In most of them the calcification was accompanied by vascular fibrosis only (Fig. 237). Active inflammation was seen in three cases only being patchy in distribution in two (Fig. 238) while in the third it was accounted for by the presence of definite subacute bacterial endocarditis. It is therefore quite possible that rheumatoid arthritis itself causes inflammation of the mitral valve which resembles the subcutaneous nodule in some cases only, but is nonspecific in character in others and leads to scarring and calcification macroscopically indistinguishable from that of true rheumatic disease.

Another lesion which appears to be caused in some cases by rheumatoid arthritis is arteritis. Reference was made previously (p. 311) to the occurrence of lesions in the heart like those of polyarteritis nodosa in two out of a series of 66 cases of rheumatoid arthritis. The lesions in the heart Case 17 in the present series (Figs. 222-225, pp.336-7) were a subacute arteritis with destruction of elastic and medial tissue. Such changes/

Heart in Healed Rheumatic Valvulitis.

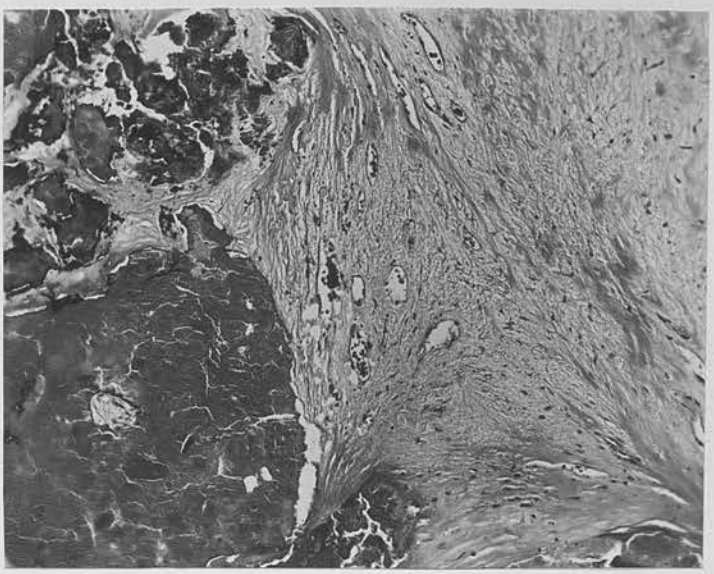

Fig. 237. Case 465 x 100. Posterior cusp of mitral valve. Extensive calcification accompanied only by fibrosis and many capillaries. Compare with Fig. 205, p. 319.

Fig. 238. Case 485 x 100. Posterior cusp of mitral valve. Patchy round cell infiltration accompanies extensive calcification. It is much less extensive and intensive than in Fig. 205, p.319. Much hyaline fibrous tissue and several thick walled arterioles are also seen.

changes were found also in the muscles (Figs. 165-166, p. 240) and nerves (Fig. 198, p. 292) of this case, in the absence of any satisfactory aetiological factor other than the arthritis. (Although the patient had a toxic reaction to gold three weeks before death, arteritis is not a known complication of chrysotherapy). Arteritis in the muscles in rheumatoid arthritis has been recorded previously (Sokoloff et alii, 1951) and was seen in this study (See Section IV). Arteritis in the nerves was also seen in this study (See Section V). There is thus evidence that rheumatoid arthritis causes arteritis in various tissues. This is supported by the fact that five other cases in this series had evidence of previous arteritis in the heart in the absence of conclusive evidence that this had been rheumatic in origin or was part of a generalised arteritis (Table LXX, Cases 13, 23, 28, 35, 117).

It must be concluded, then, that some of the cardiac lesions which occur in rheumatoid arthritis are caused by that disease rather than by previous rheumatic carditis, and that the end stage of the "rheumatoid " lesions may be indistinguishable from the end-stage of the " rheumatic " lesions. Consequently, many of the cases which have hitherto been regarded as rheumatoid arthritis with superadded rheumatic heart disease may have suffered from the former alone. Because the rheumatoid nodular lesion is the only one distinctly

different/

different from all the others encountered, Case 1 remains the only one in which the lesions can be attributed definitely, to the rheumatoid arthritis. But, according to the arguments advanced above the lesions in another 15 cases can be regarded as compatible with a similar aetiology, that is all the cases with " rheumatic " lesions except those with a history of rheumatic fever or Aschoff bodies in the heart. Morphological study alone cannot decide the aetiology of those cases in which only the end-stage of once active lesions occur.

SUMMARY.

1. The literature on cardiac lesions in rheumatoid arthritis has been reviewed with special reference to the occurrence of lesions of rheumatic heart disease. These have been recorded at autopsy in roughly one third of cases, but in a third of these clinical features were absent. In a few cases of rheumatoid arthritis cardiac lesions of a specific type have been recorded and in others lesions which could have been caused by several factors.

2. The objects of this study were to investigate the discrepancy between the pathological and clinical incidences of rheumatic heart disease in fatal cases of rheumatoid arthritis and to attempt to determine to what extent the cardiac lesions encountered in rheumatoid arthritis are caused by that disease rather than by rheumatic heart/

heart disease.

3. The heart has been studied pathologically in 61 fatal cases of rheumatoid arthritis, 49 of active rheumatic carditis, 6 of active rheumatic carditis plus subacute bacterial endocarditis, 199 of healing or healed rheumatic carditis, and 16 of healed rheumatic carditis plus bacterial endocarditis.

4. The pathological criteria used in diagnosis of rheumatic heart disease were stated.

5. Lesions which fulfilled the criteria usually regarded as diagnostic of rheumatic heart disease were present in 10 cases of rheumatoid arthritis (16%). In a further eight cases lesions compatible with rheumatic heart disease were found. Lesions resembling the subcutaneous nodule of rheumatoid arthritis were found in one case.

6. Clinical features indicative of the cardiac involvement were absent in 4 of the 10 cases in which rheumatic heart disease was found at autopsy. Examples were cited of a similar discrepancy in uncomplicated rheumatic heart disease.

7. The specificity of the lesions found in rheumatic heart disease was discussed with the conclusion that several of them are non-specific, for example, arteritis, pericarditis and myocarditis without Aschoff bodies.

8. Reasons were given for considering rheumatoid/

rheumatoid arthritis itself responsible for valvulitis and arteritis but it was not possible to state in what proportion of the cases studied rheumatoid arthritis or rheumatic fever was responsible for the lesions seen.

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APPENDIX.

The total number of cases used in the preparation of this thesis - 1543 - is so large that it was considered impracticable to abstract them all in detail. They are distributed among the various diseases as follows :-

Rheumatoid arthritis	195	(9)
Ankylosing spondylitis	14	(1)
Osteoarthritis	33	(0)
Gout	3	(1)
Rheumatic fever (including 228 heart only	276	(1)
Systemic lupus erythematosus	5	(1)
Dermatomyositis	7	(1)
Scleroderma	5	(1)
Polyarteritis nodosa	18	(1)
Non-rheumatic diseases	1019	
(including synovial tissue	368	(1)
nodules	112	(0)
muscle	419	(0)
nerves	120	(0)

Representative cases from each of these groups will be abstracted in full to a total of 17 cases as indicated in the brackets. Only very brief details will be given about the remaining cases in order to save space : fuller details were obtained about most of them and are available in note form in the writer's possession. The cases will be grouped in the first place according to diagnosis and under each disease the cases used in each section of the thesis will be recorded.

RHEUMATOID ARTHRITIS.

SECTION I.

Case 1. Jessie S. aged 74.
Admitted 18.11.47 to Northern General Hospital (Ward 2).
Died 16.7.48.
Autopsy 17.7.48 by the writer (MHA 2842).
Abstract of Case Notes :-

Rheumatoid arthritis of nine years duration. 1939 treated with gold, but developed rash, and gold was stopped. Had "pool baths". 1941, admitted Western General Hospital for 6 weeks, and was treated with wax, heat and electric treatment, then exercises. Sent home after 9 weeks. The stiffness and disability returned, and she became helpless, and by 1946 was completely bed-ridden. Previous illness : Scarlet fever.

On examination : Typical changes of rheumatoid arthritis of hands, shoulders, hips and knees. Hips and knee joints fixed in flexion.

Other/

Other systems : Enlargement of heart to left and mitral systolic murmur.

H.B. 85%, R.B.C. 4.6. B.S.R. 55 mm/hr. Urine clear. W.R. -ve. B.U.N. 10 mm.

13.4.48 : Developed episcleritis of right eye. Treated with pilocarpine.

22.1.48 : Muscle biopsy performed. Reference MHB. 2626.

7.5.48 : Puncture of right shoulder.

Developed terminal pneumonia on 15.7.48.

Macroscopic findings :

The body was that of an elderly emaciated woman. All the limbs presented deformities of shape and posture characteristic of rheumatoid arthritis, and the joints were rendered unduly prominent because of marked wasting of the muscle masses. The joints which appeared to be most affected were the shoulder, elbow, wrist and knee joints, and also the small joints of the hands. The fingers were extended at interphalangeal joints and flexed at metacarpo-phalangeal joints. The subcutaneous tissues around the elbow and knee joints were puffy owing to the accumulation of oedema fluid.

Head was not examined.

Mouth and pharynx : healthy.

Neck & Thorax : Thyroid : atrophic with areas of fibrosis.

Larynx, trachea and left main bronchus were healthy. Right main bronchus was congested. Pressure on the lungs expelled frothy oedema fluid into the bronchi.

Left pleural sac contained approximately 300 cc. of serous fluid.

Right pleural sac contained fibrous adhesions at the apex, base and along the posterior borders. There was a slight excess of serous fluid.

Lungs were of average volume. They were heavy and the posterior parts and lower lobes contained much oedema fluid. The posterior part of the left lung was partially collapsed, but the anterior borders of both lungs were emphysematous.

Pericardial sac contained approximately 20 cc. of serous fluid. A few fibrous plaques were present on the epicardium of the anterior aspect of the right ventricle.

Coronary vessels were considerably narrowed by atheroma.

Heart showed moderate dilatation of all chambers. Left ventricle showed moderate hypertrophy. The myocardium was pale and flabby, but no structural abnormality was present.

Aorta showed fairly severe atheroma with ulceration and superficial films of thrombus.

Oesophagus was healthy.

Abdomen : Peritoneal sac was healthy.

Stomach and intestines were apparently normal.

Spleen was slightly enlarged. The pulp was congested and soft and the Malpighian bodies were swollen suggesting the presence of infection.

Liver/

Liver was of average size and normal shape. The parenchyma showed exaggerated red and yellow mottling suggestive of venous congestion.

Gall bladder and biliary passages were healthy.

Pancreas and adrenal glands were healthy.

Kidneys : capsule was stripped without difficulty. The cortex was reddish brown and showed early fine granularity and its depth was slightly reduced. Arcuate vessels were thick-walled and gaping. Medulla and urinary passages showed nothing of note.

Genital organs : N.A.D.

Joints : Right shoulder and knee joints were removed for more detailed examination. In the former, a few ccs. of reddish brown fluid were taken for bacteriological investigation.

Addendum to Report : Heart : The cusps of the mitral valve and the auricle and ventricle adjacent to the posterior one were cut at intervals of 2-3mm. Midway along the posterior cusp was found a circular patch 2 mm. in diameter and consisting of white tissue with two yellowish central areas. The chordae attached to this part of the cusp were thickened by similar white tissue containing at least one more yellow zone. The free part of the cusp in this region and elsewhere was healthy. Elsewhere there was fibrous thickening of chordae, some showing central yellow zones. In the anterior cusp one or two similar areas of fibrous thickening with central yellow areas were seen.

Right knee : The joint space was almost completely obliterated by fibrous ankylosis in which small spicules of bone could be seen. The ankylosis was most marked between patella and femur which were bound together throughout their contiguous surfaces, but was also well marked between femur and tibia. The remaining articular cartilage was very irregular with considerable reduction in thickness. In many places no synovial membrane could be seen and elsewhere it showed slight hyperplasia. Patches of haemorrhage were seen in the membrane and elsewhere. The menisci were much reduced in size. The bone was very soft - it could be pitted by manual pressure - and showed very slight osteophyte formation.

Right shoulder : the outer parts of the joint surfaces were covered by a layer of fibrous tissue with moderate loss in depth of cartilage whereas the inner parts were completely disorganised, the cartilage being completely replaced by soft tissue. No osteoarthritic changes were seen. On the inner surface of the scapula, below and medial to the glenoid was a large bursa filled with yellow necrotic material. This bursa had no obvious connection with the joint cavity.

Microscopic findings :-

Heart (Figs. 230,-236). Blocks were taken from the right auricle, right ventricle, left auricle ; posterior cusp of mitral valve and adjacent ventricle and auricle (3), anterior cusp of mitral valve./

valve, anterior wall of left ventricle (2), and interventricular septum.

The outstanding lesions are in the mitral ring, mitral valve and its chordae tendineae, where lesions similar to the subcutaneous nodules of rheumatoid arthritis are seen. There are usually several foci in each section with a central necrotic area corresponding to the yellow zone noted macroscopically. Within these areas there are large quantities of granular eosinophilic material and nuclear remnants. A good many collagen fibres are also seen, usually continuous with those in the surrounding tissue. Many of these fibres are swollen, intensely eosinophilic and stain red with Masson's stain, others though swollen still stain green and a few are apparently healthy. Under polarised light fibres can be seen which are continuous on either side with the surrounding tissue and run right through the foci. Fragments of elastic tissue are also seen in some of the foci.

Surrounding these areas completely or partially is a zone of cellular collagenous tissue with a definite tendency to radial arrangement of cells and fibres. As already noted, the fibres are continuous with the central area. The number of cells varies, but in all sections examined large mesenchymal cells predominate. Some are recognisable as fibroblasts, some as histiocytes and some as myocytes, but others are undifferentiated. The myocytes are often large cells of Aschoff type and are quite frequently multinucleate. Some of these mesenchymal cells are in mitosis. Smaller numbers of lymphocytes and plasma cells are seen in this zone.

Outside this "palisade" layer is an incomplete one of densely packed lymphocytes, plasma cells, histiocytes and myocytes, roughly in that order of frequency. These cells are particularly dense in one place just under the surface of the valve. A variable number of capillaries is present in this zone, which tails off gradually into the adjacent valve or myocardium. The superficial muscle fibres have been involved in it for they are markedly atrophic and contain an excessive amount of lipochrome. There is also some diffuse fibrosis in the adjacent myocardium.

Fibrosis is also seen in the endocardium of the left auricle. In this region there are also two adjacent localised collections of large cells of Aschoff type surrounding swollen but not necrotic collagen fibres.

The above description covers the foci in the posterior cusp and the chordae, but in the anterior cusp, the process is not so well defined, being more a diffuse valvulitis with focal accentuation, lymphocytes and plasma cells predominating with numerous dilated and congested capillaries. Small plaques of calcium are present at the root of the aorta which is included in this section, but no calcification is seen in relation to the focal lesions/

lesions.

Most of the free part of the valve is more or less healthy, though the outermost zone is prolonged into it at places. Near the root there is patchy vascularity and arterioles in such places often show endarteritis obliterans. In one section of the free part of the posterior cusp there is diffuse infiltration with moderate numbers of round cells and excessive numbers of capillaries. No vegetations are seen.

At one point in the angle between two chordae, a small fibrinoid patch is seen without any reaction.

The other lesions seen in the heart are occasional tiny loose focal infiltration with lymphocytes, plasma cells and a few polymorphs in the interstitial tissue. These are seen in the auricles and are not related to collagen damage. Early atheroma with slight narrowing of lumen is seen in the anterior descending branch of the left coronary artery.

Lung : A single section shows only congestion and oedema

Liver : Well-developed chronic venous congestion.

Kidney : Moderate congestion in the medulla and very early benign nephrosclerosis.

Spleen : Chronic venous congestion and moderate enlargement of Malpighian bodies without any special features.

Skeletal Muscle (Fig. 155). Blocks were taken from rectus femoris, pectoralis major, diaphragm, deltoid, quadriceps, psoas, gastrocnemius and tongue (2). Focal collections of round cells are seen in the pectoral and diaphragm. In the former, two small perimysial foci are present, one purely lymphocytic and one with lymphocytes and plasma cells in equal numbers. In the diaphragm the infiltration is slight and confined to the areolar tissue beneath one serous surface. Some of the cells here are within lymphatics rather than loose in the tissues. Marked diffuse atrophy has occurred in pectoral, quadriceps, psoas and gastrocnemius where fibres are small with apparent increase in numbers of nuclei sometimes with clumping. In the quadriceps and psoas there is an increase in perimysial fibrous tissue. In the tongue the only abnormality is diffuse lymphocytic infiltration of the subepithelial tissue.

Peripheral Nerve : Five blocks were taken from brachial plexus and one from femoral nerve. No abnormality is seen in single sections from each block.

Synovial Tissue (Fig. 52). Two blocks were taken from the thickened membrane and capsule of the right knee. A section from one of these shows capsular tissue with no special features. In the other there are no recognisable synovial cells, but internal to the capsule is a layer of well-developed fibrous tissue 1 mm. thick containing numerous vessels of varying size. A few large focal collections/

collections of lymphocytes, plasma cells and histiocytes are seen in this tissue usually in the neighbourhood of vessels. Early medial calcification is present in the largest artery. The capsule and extra-capsular areolar tissue are healthy.

Two blocks were taken from the right shoulder and one from the bursa. Sections from each all show a similar appearance. In the joint, the free surface is lined by loose fibrous tissue up to 2 mm. thick containing many capillaries and freely infiltrated with lymphocytes, plasma cells and histiocytes, many of the latter being foamy and others containing haemosiderin. Parts of the connective tissue have undergone fibrinoid change. Occasional small foreign body giant cells are seen and in one place there is a patch of necrosis deep to the surface surrounded by the cells described above but with a definite tendency to radial arrangement. Deep to the surface several large focal collections of round cells are seen, most of them containing numerous congested capillaries. Throughout the deeper part of the connective tissue foamy histiocytes are very numerous.

A piece of muscle attached to one of the sections shows several endo- and perimysial foci such as are described in the pectoral.

In the bursa the superficial zone is broader - up to 3 mm. thick - and has undergone extensive necrosis. In places the remains of blood vessels can be seen and elsewhere, fragments of skeletal muscle. Foamy histiocytes are particularly numerous in this necrotic zone. Their contents stain with Scharlach R. and are doubly refractile. Fragments of calcified material are seen in the deeper connective tissue which resembles that already described in the shoulder and in one place several foreign body giant-cells surround a microcyst containing coagulated serous fluid.

Bones : A section from the right femoro-patellar ankylosis shows complete loss of joint space. The bones are lined by a layer of excessively cellular and quite irregular hyaline cartilage which varies considerably in thickness, being absent altogether in places. Between the cartilage layers there is dense fibrous tissue. The subchondral bone plates are extremely thin with several large gaps on either side where either cartilage or fibrous tissue is continued into the adjacent cancellous bone for a short distance. In places the subchondral plate has been recently formed by direct metaplasia from the adjacent cartilage. Inflammatory cells are scanty, occurring only in the marrow spaces, where occasional osteoclasts are also seen. The cancellous bone is very atrophic. (Photograph and lantern slide).

Sections from a block taken from the right tibia and two from the head of the right humerus show complete or almost complete destruction of the normal articular surfaces and replacement by a zone of fibrous tissue up to 4 mm. thick. In places this tissue is superficially highly vascular and contains very/

very many active fibroblasts and small numbers of round cells, the collagen fibres being very fine whereas deeper it is much more fibrous, i.e. it resembles ordinary granulation tissue. Elsewhere the tissue is less vascular and cellular. Where cartilage is still present it is thin and has lost its normal architecture. At the junction between fibrous tissue and bone osteoclastic absorption is seen. Scattered through the granulation tissue are areas of fibrinoid change, most marked towards the surface. The connective tissue frequently extends through breaches in the atrophic bone and into the underlying cancellous bone. In the connective tissue, early cartilaginous metaplasia is sometimes seen. Patchy, thickening of the bone is seen in the tibia and here and there naked bone is exposed and is undergoing eburnation.

Pathological diagnosis:

Severe rheumatoid arthritis involving shoulders, wrists, hands, hips and knees.
" Rheumatoid " endocarditis of mitral valve.
Left ventricular hypertrophy.
Pulmonary oedema.
C.V.C. liver, spleen and kidneys.
Lymphorrhages in skeletal muscles and marked muscular atrophy.

Case 2.

Andrew N. aged 63.
Admitted 19.10.44 to Northern General Hospital, Ward 2.
Died : 20.6.48.
Autopsy 21.6.48 by the writer (MHA 2812).
Abstract of Case Notes :- Rheumatoid arthritis began with pain in both feet in 1938, followed by pain in his shoulder joints and knees. Treated in Dublin in 1933 with serum injection and radiant heat. Able to work to 1938, when another exacerbation treated in R.I.E. In 1943 had to give up work again owing to pain and swelling of both knees. He had a marked rheumatoid deformity of both wrists and hands, and commencing flexion contractures of both knees. He was treated with several courses of gold, manipulation of wrists, and plaster shell and traction to knees. In March 1947, and October 1947 he had attacks of right basal pneumonia with failure of complete resolution. In the middle of November, 1947 he began to complain of sore throats, and difficulty in swallowing and he did not look so well since then. Strep. viridans isolated from throat swab, sore throats continued in spite of treatment fluctuating in intensity. Voice gradually changed and became weaker and husky, swallowing became painful. Chronic cough and greenish sputum - normal respiratory flora on bact. examination. No T.B.
O.E. Gross rheumatoid arthritis deformities of hands, elbows and feet with bilateral hallux vulgus. Several/

Several hard nodular glands felt in front of and behind the sternomastoid on both sides of the neck. Knees flexed to 90°.

Macroscopic findings :-

The body was that of a very wasted, elderly man of small stature. Generalised muscular wasting was present. Both shoulders showed limitation of movement, particularly abduction, fairly marked crepitus being present on movement of the joint. A flexion deformity of both elbows was present so that neither could be straightened to more than 150 degrees. Crepitus was present on movement of both wrists, while the hands showed very marked ulnar deviation of the fingers with subluxation of the metacarpophalangeal joints. A moderate degree of spindling of the proximal interphalangeal joint was present. In the lower limbs both knees showed a very marked flexion deformity the joints being held at about 90 degrees, while movement was limited to about 10 to 15 degrees from this position. The knees stood out rather prominently, but this was due more to atrophy of the surrounding muscles than to swelling of the peri-articular tissues.

Serous Cavities : Peritoneal cavity was healthy, but both pleural cavities and the pericardial cavity were almost completely obliterated by dense fibrous adhesions of long standing.

Cardio-vascular System : Heart 240 gms. The heart was a little small for the size of the body, but showed no other abnormality on external examination apart from the remains of the adhesions. Section showed a moderate degree of brown atrophy of the myocardium, but there was also a mottled pallor suggestive of fatty degeneration. The endocardium showed no evidence of old or recent endocarditis.

The coronary vessels showed a moderate degree of atheromatous change, but the lumen was patent throughout.

Aorta showed fairly widespread and marked atheroma.

Respiratory System : Larynx, trachea and bronchi were healthy.

Lungs - right 580 gms. left 500 gms. Both lungs were normal in size and shape, but showed a considerable amount of oedema on section, in the right lower lobe, a rather more rubbery consistence suggesting that some consolidation was superimposed upon oedema.

Alimentary System : Mouth, tongue, pharynx : the pharyngeal wall at the level of the inferior constrictor showed some thickening and replacement of the muscle fibres by rather firm white tissue. This had the appearance rather of the fibrous tissue than of tumour. Posterior to the pharynx and lying on the anterior surface of the lower cervical vertebrae was a small nodule about 1 cm. in diameter and consisting of similar tissue with a small cystic space in the centre.

Oesophagus/

Oesophagus, stomach and intestines were healthy.

Liver, 1,360 gms. The liver was normal in size and shape showing no abnormality on external examination, while on section the only change noted was some pallor of the parenchyma.

Gall bladder, biliary system and pancreas were healthy.

Urogenital system : Kidneys right 160 gms., left 140 gms. The kidneys were normal in size and shape showing no abnormality on external examination or on section.

Lymphatic and Haemopoietic System : Spleen - 380 gms. The spleen was considerably enlarged and soft in consistence though it had retained its normal shape. On section the pulp was seen to be soft and pale, but the architecture was in the main preserved.

Lymph glands in the axillae, groin, root of neck and para-aortic regions were nearly all slightly enlarged and showed on section a reddish pink colour, the appearances being those of reactive hyperplasia.

Endocrine System : The thyroid gland was healthy, but on the anterior surface of the thyroid cartilage in the midline just above the isthmus of the thyroid gland was a small nodule consisting of rather firm, homogeneous white tissue with a small space in the centre. It is suggested that this may be the remains of an old thyroglossal cyst.

Suprarenals were healthy.

Locomotory System : Both knee joints were dissected out and had similar appearances. The joint space was greatly reduced due to the formation of firm fibrous adhesions between the synovial membrane and the bone in all areas except those in which bony surfaces were in apposition. Even in these areas very little space existed between the bony surfaces and no free fluid, apart from small quantities of blood, was seen in either joint. Great loss of articular cartilage had occurred from the opposing bony surfaces, considerable areas of which were covered by reddish brown tissue continuous with the remains of the synovial membrane. Elsewhere the synovial membrane showed several areas of yellowish brown colour indicative of old haemorrhage, but there was very little remaining hypertrophy. A slight degree of lipping of the edges of the articular surface of the femur was seen.

The right shoulder was also dissected showing very similar changes with obliteration of the joint space apart from a small area where the articular surfaces of the humerus and scapula were in contact. Again considerable loss of cartilage had occurred.

All muscles in the regions examined were reduced in size and very pale in colour.

Microscopic findings :-

Heart : (Figs. 216 - 218). Blocks were taken from right auricle, right ventricle, left auricle, mitral valv e and adjacent auricle and ventricle, left ventricle (2), interventricular septum and aortic valve/

valve.

The epicardium is everywhere thickened by collagenous tissue with capillary congestion and focal perivascular and perineural collections of lymphocytes and plasma cells in the deeper part, and in places deposits of yellow-brown pigment. In the myocardium two types of change are seen :-

(a) fibrosis, which is present in both auricles to a marked degree and to a slight extent around vessels in the left ventricle, and (b) inflammatory lesions, which are present in both ventricles, being much more marked on the left side, particularly near the mitral ring. Here the interstitial spaces are distended by a fairly widespread infiltration with polymorphs, myocytes and occasionally eosinophils, for the most part diffusely distributed but here and there focal. The foci are often associated with swelling of collagen and occasionally there is fibrinoid necrosis of the collagen fibres. Small arteries and arterioles in the affected area do not bear any special relationship to the foci. Some distance from the acute lesion several focal collections of lymphocytes and plasma cells are seen in the interstitial tissue.

The mural and valvular endocardium and the valves in the sections examined are healthy. A large coronary artery in the epicardial fat near the mitral ring shows early atheroma with slight narrowing of its lumen (Subsequent naked eye examination showed a grey-brown colour in the myocardium of the left ventricle near the acute myocarditis. Several similar areas were seen elsewhere in the left ventricle).

Lung : Most of the section examined shows oedema only, but here and there one or more alveoli contain polymorphs as well, indicative of an early bronchopneumonia.

Trachea and pharynx (Fig. 108). Several blocks were taken from the 'fibrous tissue' in the wall of the pharynx, on the anterior surface of the thyroid cartilage and on the anterior surface of the cervical vertebrae. All are very similar, consisting of very cellular fibrous tissue which has infiltrated between the muscle fibres of the pharyngeal wall. In most places the collagen fibres are healthy but in two or three areas they are necrotic and surrounded by intensely cellular zones of fibroblasts, lymphocytes and polymorphs with a tendency to radial arrangement. The largest of these necrotic areas measures 3 x 1 mm. Mitosis is not infrequent in the fibroblasts. Apart from these foci many smaller collections of polymorphs and swollen fibroblasts are seen without any change in the collagen fibres and sometimes collagen fibres are swollen and deeply eosinophilic without any cel lular reaction. Capillaries and small arterioles are numerous often with a dense cuff of lymphocytes and histiocytes.

The trachea shows dense round cell infiltration and excessive fibrosis in the mucous and submucous layers with loss of the epithelial cells. Outside

the tracheal wall cellular fibrous tissue as above is seen with dense round-cell cuffing of the vessels. Near the ossified cartilage is an excessively cellular area with a small central focus of granular necrosis staining deep blue.

Liver : Several small focal collections of intra- and extra-cellular yellowish-brown pigment are scattered irregularly through the section. The cells involved are mainly histiocytes. In one or two of these foci liver cells have disappeared and there is an associated round-cell and polymorph infiltration.

Pancreas : Apart from hyaline thickening of the walls of some arterioles and occasional foci of lymphocytes in the interstitial tissue, no abnormality is seen. The hyaline material in the arteriole walls stains a much deeper red than the amyloid in the kidney and spleen.

Kidney : Many glomeruli are less cellular than normal and partially or completely replaced by pale pink hyaline material. Similar material, all of which takes up Congo Red is seen in the thickened Bowman's capsules, a few afferent arterioles and many interlobular and arcuate arteries. The tubules are not much affected, and no gross scarring is seen. There is patchy round cell infiltration in the cortex whereas the pelvic mucous membrane is diffusely infiltrated and markedly congested with some haemorrhage. There is thus a definite pyelitis.

Bladder : The mucous membrane is markedly infiltrated with round-cells both diffusely and in dense foci one or two of which are also seen in the muscle coat. Vessels are deeply congested.

Spleen : The Malpighian corpuscles are replaced to a varying extent by pale pink hyaline material similar to that in the kidney and also taking up Congo Red. Many of the arterioles have deposits of the same material in their walls. Apart from this there is moderate congestion of the pulp.

Lymph Nodes : Sections from two axillary nodes show a considerable increase in the number of lymphoid follicles all of which are markedly reactive with a large central area, in which both proliferation and degeneration of cells is seen, and a narrow rim of lymphocytes. There is some hyperplasia of reticulum cells in the medulla and capillaries are numerous and congested. A hilar node on the other hand has a few small inactive follicles whereas all the sinuses are distended with histiocytes, lymphocytes, plasma cells and a few polymorphs. Many of the histiocytes carry carbon pigment, a few carry light yellow-brown material.

Skeletal Muscle (Figs. 152, 154). Blocks were taken from pectoralis major, diaphragm, psoas, right deltoid, right quadriceps (2) and tongue (2). All sections examined contain dense foci and lymphocytes, plasma-cells and histiocytes, situated between muscle fibres and in the interstitial tissue. The foci are most numerous in the left adductor magnus where 31 are seen in a section measuring 14 x 13 mm. Nearly all have an arteriole or capillary/

capillary in the centre with lymphocytes most numerous in the closely packed zone around it and the other cells more conspicuous towards the more loosely arranged periphery. Many of the foci are clearly visible on naked eye examination of the sections, and one or two of the largest, in left adductor magnus have a structure resembling a lymphoid follicle, in that the central area is rather loose and consists of large cells of reticulum-cell type and lymphocytes, many of which are degenerating. Around this area which also contains a congested arteriole there is a dense rim of lymphocytes and a few reticulum-like cells. No collagen fibres are seen in the endomysial foci and no damage to those fibres in the perimysial foci.

Degenerative changes are present to a varying degree but are independent of the round-cell foci. They are most marked in sections from right and left quadriceps where the muscle fibres are reduced to one quarter of the normal width with great increase in the number and size of subsarcolemmal nuclei which often lie in longitudinal rows or in clumps. Striations are preserved even in these atrophic fibres.

Both sections of the tongue are much less affected by either of these changes than the other muscles. Thus, though there is marked diffuse and focal round-cell infiltration just beneath the epidermis, only one or two small foci are seen deep in the muscle. Atrophic changes are minimal.

Synovial Tissue : Blocks were taken from the right knee and right shoulder. In the knee no synovial surface remains and the section consists of collagenous connective tissue of varying cellularity, the inner edge of which is less fibrous but oedematous with small patches of fibrinoid change and deposits of yellow-brown pigment deep to the surface. Throughout the section occasional arterioles and capillaries have cuffs of round-cells such as occur in the muscles. In the section from the shoulder the joint surface is lined partly by synovial cells, partly by naked collagen and partly by necrotic tissue. The synovial cells are large, occasionally multinucleate and several layers deep, and there is gradual transition from this area to one of fibrinoid material in which early calcification can be seen. Beneath the surface the collagen fibres are greatly swollen and often hyaline with widespread lymphocytic and plasma-cell infiltration. The surrounding fibrous tissue of the capsule contains occasional round-cell foci and a branching cleft suggestive of a pocket of the synovial cavity but not lined by synovial cells.

Bone : A section from the head of the right humerus is completely devoid of articular cartilage. Towards the centre of the articular surface there is a dense layer of compact bone up to 2 mm. thick and having several irregular Haversian systems. It is more/

more cellular than the bone elsewhere. Its exposed surface lines the joint space and is mostly quite smooth, though here and there irregular cartilage replaces the bone. On either side this bone is covered by irregular fibro-cartilage which merges rapidly with cellular and vascular connective tissue which covers the remains of the subchondral plate, and infiltrates the underlying marrow spaces. The collagen fibres are fine though sometimes swollen and here and there fibroblasts are large and active with little or no collagen. Round cells are plentiful, being both focal and diffuse, especially in the marrow spaces where several well-developed perivascular foci are seen. Many congested capillaries are seen. At the interspace between connective tissue and bone, active absorption of bone by mono- and multinucleate osteoclasts is in progress, one of the mononuclear cells being in mitosis. In the underlying cancellous bone the trabeculae are much fewer and smaller than normal, and no haemopoietic marrow is seen.

On the lateral condyle of the left tibia the granulation tissue is thicker (2.5 mm.), more cellular with several areas of fibrinoid necrosis of collagen, two large areas of haemorrhage and occasional metaplasia to cartilage.

Peripheral Nerves (Figs. 191, 194). Three blocks each were taken from the left sciatic and femoral nerves and from the right brachial plexus and single sections examined from each block. All contain round-cell foci similar to those described in the skeletal muscles. The majority of the foci are in perineural connective tissue but a few show spread into the nerve bundles. The largest foci are visible on naked eye examination of the slides. The structure of all is the same as in muscle with the exception that in one large focus some collagen fibres are swollen, though not necrotic and histiocytes in some of the foci in the sciatic nerve contain granular yellow pigment which gives the Prussian Blue reaction.

Pathological diagnosis :

Advanced rheumatoid arthritis affecting hands, wrists, elbows, shoulders, knees and left hip.
Adhesive pericarditis.
Acute myocarditis.
Old pleurisy.
Pulmonary oedema with early hypostatic pneumonia.
Focal necrosis of liver.
Early amyloidosis of kidneys and spleen.
Splenomegaly and generalised enlargement of lymph nodes.
Pyelitis and cystitis.
Lymphorrhages of skeletal muscles and peripheral nerves.
Chronic inflammatory lesion of pharyngeal and laryngeal regions (rheumatoid nodule).

Case/

Case 3.

F. aged 55. Ref : LI/ 2081.
Rheumatoid arthritis (RA) of 10 years' duration affecting hands, knees and ankles. Tissue obtained at arthrodesis of right knee.

Case 4.

F. aged 58. Ref :- P.M. 259/48.
RA of 12 years' duration affecting ankles, hands and elbows. Death from viral encephalitis.
Synovial tissue obtained from left shoulder, acromio-clavicular joint and knee.

Case 5.

F. aged 64. Ref :- EHB 2323.
RA of 20 years' duration affecting nearly all limbs joints. Tissue obtained at arthrodesis of knee. (Figs. 1, 2 and 4).

Case 6.

F. aged 49. Ref :- MHB 3042.
RA of 18 years' duration affecting hands, knees, ankles and feet. Tissue obtained at arthrodesis of right knee.

Case 7.

F. aged 75. Ref :- MHA 2785.
RA of 2 years' duration, affecting all limb joints. Autopsy disclosed no other lesions except marked wasting and recent haemchagic cystitis. Synovial tissue obtained from right knee and shoulder.

Case 8.

F aged 85. Ref :- MHA 2804.
RA of 8 years' duration affecting shoulders, elbows, wrists, hands, knees and ankles. Death from cardiac failure. Synovial tissue obtained from right knee.

Case 9.

M aged 70. Ref :- MHA 2814.
RA of 8 years' duration affecting many joints. Death from advanced pulmonary tuberculosis with tuberculous enteritis and colitis : also chronic active duodenal ulcer. Synovial tissue obtained from right elbow.

Case 10.

F aged 71. Ref :- PM. 461/48.
RA of several years' duration. Exfoliative dermatitis/

dermatitis following chrysotherapy. Death from uraemia due to chronic pyelonephritis and renal amylcidosis. Synovial tissue obtained from right knee.

Case 11. M

M aged 52. Ref :- XXXIX/ 623.
RA of two years' duration affecting elbows, wrists, hands, knees and ankles. Tissue obtained at biopsy of right knee.

Case 12.

F aged 63. Ref :- PM. 480/ 48.
RA of 32 years' duration affecting all limb joints. Death from paraplegia following transverse myelitis caused by organisation of subarachnoid haemorrhage following fractured skull : also benign nephrosclerosis. Synovial tissue obtained from right knee.

Case 13.

Mrs. Christina C. aged 32.
Admitted 25.10.49 to Royal Infirmary, Ward 14 (Case 11368).
Died 26.10.49.
Autopsy 27.10.49 by the writer (PM. 515/48).
Abstract of Case Notes :- Rheumatcid arthritis 4 years since birth of last child. Flexion contracture knees 2½ years. Swelling of legs 5 days, blistering 3 days. Irritating cough. Tachycardia. Patient had only been in Ward for half day. Grew restless and rather noisy. 5 minutes later when looked at was found to be dead. Previously admitted to Western General Hospital on 20.7.45 (Case 17804) with stiffness of elbows, knees and hands for 7 months. On examination the skin of hands, forearms, elbows and knees was fixed to the underlying tissues : flexion deformity of fingers, elbows, and knees. BSR 50, Hb. 69%, R.B.C. 3,700,00 per cmm., WBC 11,200 per cmm.
Diagnosed at first as dermatomyositis but later as rheumatcid arthritis when joint involvement occurred.

Macroscopic findings :-

The body was that of a young woman of average height and bodily build but showing considerable wasting of musculature all over the body and particularly in all four limbs. The changes were most marked in the hands, in both of which very gross muscular wasting was present. All the fingers showed ulnar deviation at the metacarpo-phalangeal joints, but no evidence of ankylosis. There was no obvious spindling of any of the fingers, though movements/

movements at the interphalangeal joints were considerably limited. Movements at the wrist joint was limited to about 20° of flexion. Flexion contractions were present at both elbows and very little movement was possible at the shoulder joints. The lower limbs showed flexion deformities of both knees, extension beyond 120° being impossible due to soft tissue contractures. Marked oedema of both legs below the knees was present and several large blisters were present over both lower legs and feet. Oedema was also present over the sacrum. Small areas of ulceration were present over one or two bony prominences, such as the right olecranon and right patella.

Serous Sacs : All serous sacs contained a considerable quantity of clear serous fluid, there being about 500 cc. in the peritoneal and each pleural cavity, and 200 to 300 cc. in the pericardial cavity.

Cardio-vascular System : Heart 360 gms. Showed considerable prominence of the right ventricle, but no other abnormality was noted on external examination. On section considerable dilatation and hypertrophy of the right ventricle was found, but the other chambers appeared to be normal in size. The tricuspid valve admitted 5 plus fingers, mitral valve 3 fingers. None of the valves showed any evidence of old or recent endocarditis. Coronary arteries were healthy.

Aorta : showed fairly extensive, but early atheromatous changes limited to the posterior aspect. No evidence of thrombosis was found in any peripheral veins.

Respiratory System : Larynx, trachea and bronchi : Were healthy.

Nasal sinuses : were examined and showed no abnormality of their mucous membrane, the cavities in all cases being empty.

Lungs : R 440 gms. L 340 gms. Lungs had collapsed as a result of the effusions but did not show any other significant abnormality on external examination. On section a moderate degree of oedema and also of congestion were noted, but there was no evidence of bronchopneumonia.

Alimentary System : Mouth, tongue, pharynx, oesophagus, stomach and intestines : Were healthy.

Liver : 1460 gms. Was normal in size and shape, but firmer in consistence than normal, while through the capsule the parenchyma had a mottled appearance. This was confirmed on section, which revealed an advanced degree of chronic venous congestion.

Gall bladder, biliary system and pancreas : Were healthy.

Urogenital System : Kidneys : R 140 gms. L 160 gms. Kidneys were normal in size and shape showing no abnormality on external examination. On section a slight degree of congestion was seen, more marked in the medulla than in the cortex, so that differentiation of the two was not difficult. No undue/

undue prominence of vessels was seen. Capsules stripped without much difficulty but on the right side considerable coarse scarring of the cortex was present. There was no definite indication whether this was due to primary renal disease or to old healed infarcts, but sections have been taken for microscopic examination.

Calyces, pelves, ureters and bladder : Were healthy.

Uterus and appendages : Were healthy.

Lymphatic and Haemopoietic Systems : Spleen 160 gms. Was slightly enlarged and much firmer than normal in consistence. Its diaphragmatic surface was adherent to the diaphragm by a number of fairly dense fibrous adhesions. On section the organ was seen to be considerably congested but no other abnormality was noted.

Lymph glands : No abnormal lymph glands were seen anywhere in the body.

Bone marrow : In the mid shaft of the femur (right) the marrow showed complete replacement of the normal fatty marrow by bright red fleshy tissue.

Endocrines : Thyroid, suprarenals and pituitary showed no abnormality.

C.N.S. : Brain : Was sectioned but showed no abnormality of meninges, vessels or parenchyma.

Locomotory System : Both shoulder joints were opened and showed considerable loss of cartilage from both humeri, the underlying bone being extremely soft, so soft that it could be dented by a finger. In a few areas where the cartilage still remained there was evidence of formation of granulation tissue on its surface. No adhesions were present between the joint surfaces. The synovial membrane was slightly congested and showed a few villous processes, but did not appear to be very grossly affected.

Both knees were examined. The right one showed no significant abnormality, while on the left side a few small areas of erosion of cartilage was seen and a small quantity of granulation tissue was present over the articular surface of the femur. The right knee was dry, while the left one contained about 5 cc. of thick turbulent fluid.

Microscopic findings :-

Heart (Figs. 215, 219-221). Blocks were taken after fixation from right auricle, right ventricle including tricuspid valve (2), left auricle, posterior cusp of mitral valve with adjacent auricle and ventricle, interventricular septum, anterior pituitary muscle and aortic valve.

In several sections, the subepicardial tissue contained small peri- or para-vascular foci of lymphocytes and plasma cells occasionally associated with swelling of fibrinoid change in collagen fibres : no Aschoff cells were seen in these foci. Coronary vessels were mostly normal - an occasional one showing early intimal thickening. Similar small inflammatory foci were seen near vessels in the myocardium/

myocardium of all four chambers with occasional polymorphs in some of them but no Aschoff cells and no necrosis of collagen. Two quite different areas - small foci of necrosis of muscle fibres with round cell and early fibrous tissue reaction - were seen in right ventricle and inter-ventricular septum. In some areas small branches of coronary vessels had thickened walls, usually due mainly to adventitial fibrous tissue. The mural endocardium was healthy : the valves showed no evidence of old or recent valvulitis.

Liver, Spleen, Suprarenals : Advanced chronic venous congestion.

Kidneys : The granularity of the right kidney was seen to be due to a well developed patchy benign nephrosclerosis. Similar, but much earlier changes were present in the left kidney.

Pituitary : congested but otherwise normal.

Pancreas : N.A.D.

Lymph gland : Marked sinus catarrh only.

Femoral marrow : The haemopoietic tissue was both erythropoietic and myelocytic in nature.

Skeletal Muscle (Figs. 148, 153, 156, 169). Blocks were taken from rectus abdominus, pectoralis major, diaphragm, psoas, deltoid and quadriceps.

All sections showed inflammatory lesions but degenerative changes were slight. The inflammatory lesions were dense foci of lymphocytes with small numbers of plasma cells and histiocytes lying in the perimysial connective tissue, between muscle fibres or in both situations. The larger ones were spindle-shaped or longitudinal on section and easily visible to the naked eye. All contained numerous capillaries : some were centred around a small arteriole. Collagen fibres were unusual in the foci and when present appeared healthy. In the diaphragm the foci were so numerous that the smallest ones gave the impression of a diffuse infiltration of the muscle and plasma cells were more numerous. In the pectoral a number of foci were in tendon, the collagen of which was swollen and deeply eosinophilic but not necrotic.

The degenerative changes bore no definite relationship to these foci. The size of muscle fibres varied but atrophy was not marked. Here and there striations stained poorly or not at all and occasionally fragmentation or lysis of a segment was seen. In only one instance a muscle fibre entered a focus and appeared to disintegrate : outside the focus this fibre was swollen and hyaline.

Synovial Tissue : Four pieces of synovial membrane from knee and one from shoulder were taken for section : all showed similar changes.

The synovial surface over large areas had undergone fibrinoid necrosis and many small villi were completely necrotic. The necrotic areas contained sparsely distributed round cells and fibroblasts often themselves degenerating. Deep to this the connective tissue contained several peri- or paravascular foci similar to those in the skeletal muscles./

muscles. Arteries and arterioles frequently had increased fibrous tissue in intima and media.

Bone : Sections from lower end of L. femur and head of humerus showed great thinning or complete loss of hyaline cartilage with necrosis and disintegration of such as was left. In places the surface was covered with well developed collagenous tissue the fibres of which were swollen, hyaline and sometimes necrotic. Occasionally the fibrous tissue was cellular and contained congested capillaries, but inflammatory cells were scarce. In the humerus areas of cartilaginous metaplasia were seen in this fibrous tissue and in some areas where the "pannus" lay directly on bone early herniation into the bone was seen. The cancellous bone was markedly atrophic with reduction of haemopoietic tissue but no granulation tissue.

Peripheral Nerves (Figs. 184, 190, 195). Five consecutive blocks were taken from a femoral nerve and from a brachial, plexus and a single section from each was examined.

Every section contained several inflammatory foci very similar to those in the skeletal muscles, many being visible to the naked eye, the largest 2 mm. long. The foci were situated in perineural connective tissue and were again predominantly lymphocytic with small numbers of plasma cells and histiocytes, containing several small capillaries or arterioles. Occasionally an arteriole or capillary arising from a vessel within a focus and running into a nerve bundle carried with it a fine cuff of lymphocytes. Many capillaries in relation to foci had swollen endothelium and occasional small arteries showed subendothelial fibroblastic increase. No degeneration of collagen was seen.

Pathological diagnosis :-

Rheumatoid arthritis.
Hypertrophy and dilatation of right ventricle.
Healed coronary arteritis and multiple small organised myocardial infarcts.
Chronic venous congestion of liver, spleen and kidneys.
Effusions in all serous cavities.
Oedema of lower limbs.
Lymphorrhages in skeletal muscles and peripheral nerves.

Case 14.

Agnes M. aged 82.
Admitted 21.4.46 to Northern General Hospital, Ward 4.
Died 13.12.48.
Autopsy 13.12.48 by the writer (MHA 3028).
Abstract of Case Notes :- Progressive rheumatoid arthritis for at least six years, affecting/

affecting all limb joints, tempero-mandibular sternoclavicular joints. The disease appeared to be burnt out, but she had periodic attacks of pain in the left knee and left shoulder. Arterio-sclerotic Parkinsonism developed during the last year or so. Death appeared to be due to exhaustion and terminal pneumonia.

Macroscopic findings :-

The body was that of a small, rather wasted old woman. Marked deformities of all four limbs were present particularly of the left knee which was flexed to about 90° with subluxation of the tibia on the femur. The left foot and ankle were considerably oedematous. Rigor mortis was only partially developed and lividity present on the posterior aspect.

Serous Cavities : The peritoneal, left pleural and pericardial cavities contained no excess of fluid and showed no abnormality.

The right pleural cavity was obliterated over much of its extent by dense fibrous adhesions. There was, however, no evidence of recent pleurisy and no effusion in the remaining patent part of the cavity.

Cardio-vascular System : The heart was normal in size and shape showing on external examination a localised area of fibrous thickening of the epicardium over the apex of the left ventricle. Myocardium was darker than normal in colour and in all chambers a little thinner than normal. All chambers were normal in size and shape, the mural endocardium being everywhere healthy. Mitral valve admitted the tips of 2 fingers and showed oedema of its cusps with slight nodular fibrous thickening particularly of the posterior cusp. The chordae tendineae were slightly thickened and shortened so that there was a slight degree of mitral stenosis. The tricuspid orifice admitted 3 plus fingers. Aortic and pulmonary valves were both healthy. The coronary vessels showed a fairly marked degree of atheroma.

The aorta and its main branches showed advanced atheromatous changes both recent, in the form of ulceration, and older lesions in the shape of extensive calcification.

The veins of the left leg were dissected out but no evidence of thrombosis was found.

Respiratory System : Larynx, trachea and bronchi were healthy.

The lungs. Both lungs were normal in size and shape showing no abnormality on external examination.

The right lung showed a small scar in the apex of the upper lobe with a tiny area of calcification. It was difficult to say whether this was tuberculous since there was no evidence of a tuberculous lesion in the regional lymph nodes. Elsewhere the right upper lobe and middle lobe were healthy. The lower lobe/

lobe was considerably congested and on further section the main artery to this lobe was found to be occluded. It was difficult to tell whether the occlusion was due to embolism or thrombus formation locally, for the vessel was occluded with rather dark, friable blood clot which was only slightly adherent to the walls of the vessel.

The left lung showed no abnormality on section.

Alimentary System : Mouth, tongue, pharynx, oesophagus, stomach and intestines were healthy.

Liver was normal in size and had a large vertical groove in the right lobe presumably a congenital abnormality. It was rather paler than normal and a little soft. On section these appearances were confirmed but in addition to the pallor of the parenchyma, generalised congestion of the tributaries of the hepatic vein was seen.

Gall bladder was very considerably distended so that in size it was about 8 times normal and on section the wall was seen to be thin but with no evidence of inflammatory change, and the bile which it contained was much paler than normal in colour.

The common bile duct was distended so that it admitted the small finger and in addition the duct contained a single pigment stone (about 1 cm. in diameter) and a quantity of biliary mud. The stone lay free in the lumen of the duct but in the absence of any other stone it is presumed that it had acted as a ball valve at the lower end of the duct.

The pancreas was atrophic but otherwise apparently healthy.

Urogenital System : The kidneys were normal in size and shape showing no abnormality on external examination. On section cortex and medulla were easily differentiated and did not show any particular abnormality. The vessels were healthy apart from moderate atheromatous changes in the main arteries. The capsules stripped cleanly leaving a surface which was only very slightly granular.

Calyces, pelves, ureters and bladder. On both sides the calyces and pelves were slightly dilated but did not show any inflammatory changes. The ureters and bladder were healthy.

Uterus and appendages. The uterus was small and atrophic, but it contained both within its wall and in the subperitoneal region several small fibroids, one of which was calcified. The left ovary was healthy while the right contained a loculated cyst measuring about 6 x 4 x 2 cm. The cyst contained thin serous fluid and had a thin, smooth, atrophic wall.

Lymphatic and Haemopoietic Systems : Spleen was normal in size and shape showing no abnormality on external examination or on section.

No enlarged lymph glands were found anywhere in the body.

Endocrine System : Pituitary, thyroid and suprarenals were healthy.

Central Nervous System : The brain was removed and examined fresh. The main cerebral arteries showed/

showed only a minor degree of atheroma. The only abnormality noted in the brain parenchyma was some loss of pigmentation of the left substantia nigra.

Locomotory System : The right shoulder and knee joints were examined, both showing a picture of burnt out rheumatoid arthritis with superimposed osteo-arthritic changes. In both there was great loss of articular cartilage with exposure of the underlying bone, and though no "pannus" was present, degenerative changes in the remaining cartilage were still active. In both joints a slight degree of osteophytic lipping was present round the margins of the articular surfaces of the bones. In the shoulder, a slight degree of hypertrophy of the synovial membrane was still present but in the knee, the inner surface of the synovial membrane was quite smooth with no evidence of hypertrophy or villous formation. In the left knee, fibrous ankylosis was also present. There was no excess of fluid in either the right shoulder or right knee.

Microscopic findings :-

Heart (Figs. 205 and 207). Blocks were taken from the lateral cusp of tricuspid valve with adjacent auricle and ventricle, septal cusp of tricuspid with ventricle and aorta, right ventricle, left auricle, posterior cusp of mitral valve with adjacent auricle and ventricle, interventricular septum and anterior papillary muscle.

The epicardium, where present, is slightly oedematous, containing occasional focal collections of lymphocytes and histiocytes with scanty myocytes and eosinophils. A main coronary artery in the right atrio-ventricular groove is considerably narrowed by well-developed atheroma and other vessels show less marked changes of the same nature. The myocardium except in the last two situations contains no inflammatory cells. In the inter-ventricular septum and to a greater extent in the anterior papillary muscle small foci of lymphocytes and histiocytes, sometimes with a few eosinophils lie around congested capillaries in septa. In one of these foci, there is hyaline swelling of collagen fibres but no necrosis. In the left ventricular myocardium adjacent to the mitral valve ring, patchy old-standing fibrosis is seen, some of the patches being around septa in which collagen is excessive and others being irregularly scattered in the muscle. Some small vessels in affected septa have fibrous thickening of their media. The muscle fibres in most sections show brown atrophy with here and there fragmentation and basophilic staining, or vacuolation. The mural endocardium is healthy. In both sections of the tricuspid valve occasional collagen fibres are swollen and deeply eosinophilic, but nuclei are healthy and there is no reaction. A small wart-like elevation on the auricular surface of the free part of the lateral cusp consists of fibroblastic proliferation in the substance of the valve/

valve with infolding of the surface and proliferation of endocardial cells, but again there is no reaction. In a section from one of the nodular patches in the posterior cusp of the mitral valve there is alternating dense fibrous tissue and intense cellular infiltration, also large areas of calcification, mainly in the fibrous patches. Most of the collagen is relatively acellular but occasionally there is swelling and hyaline change, but no necrosis. The cellular infiltration is diffuse, with focal accentuation and consists of lymphocytes, plasma cells, histiocytes and myocytes and moderate numbers of eosinophils. The plasma cells not infrequently contain Russell bodies. Numerous capillaries and a few arterioles are seen in these zones and also numbers of fibroblasts. Here and there yellow-brown pigment has been deposited.

Lung : A section from the lesion at the right apex shows a fibrous tissue band running into the lung from the apex for about 1 cm. and containing numerous widely dilated and congested blood channels. In the adjacent lung there are areas of collapse and of emphysema. The small bronchi and bronchioles are dilated and they and adjacent alveoli contain a polymorph exudate. There is no evidence of tuberculosis.

Liver : There is widespread fatty degeneration, amounting often to necrosis of liver cells, but with no definite anatomical distribution. A slight lymphocytic-histiocytic reaction has occurred. Surviving liver cells are often irregular in size and shape with large nuclei, sometimes two per cell. No mitotic figures are seen. Many of these irregular nuclei contain vacuoles. There is no distortion of lobular architecture and no fibrosis. In portal tracts there is considerable congestion and excess of lymphocytes. The degree of cellular activity is in keeping with regeneration in response to the fatty degeneration.

Pancreas : There is quite marked " pancreatosis" dilatation of acini, sometimes with a content of coagulated albuminous fluid but without any inflammatory response. The splenic artery is included in the section and shows very early atheroma.

Spleen : Apart from some congestion of the pulp no abnormal features are seen.

Kidneys : Occasional glomeruli are to a varying degree fibrosed, one showing concentric cellular fibrosis of Bowman's capsule with adhesion to the tuft. Related distal tubules contain hyaline casts and there is focal round-cell infiltration. Some afferent arterioles, interlobular arteries and arcuate arteries have moderate intimal fibrous thickening. There is a good deal of venous and capillary congestion.

Suprarenal : Occasional focal collections of lymphocytes and a few histiocytes occur in both glands in the zona fasciculata of the cortex. In the/

the left gland there is, in addition, early tubular change in the zona glomerulosa and areas in the zona fasciculata where the cells are smaller than normal with eosinophilic, non-lipoid-containing cytoplasm and nuclei smaller and darker than elsewhere.

Skeletal Muscle (Fig. 174). Blocks were taken from rectus abdominis, pectoralis major, diaphragm, quadriceps, psoas, deltoid and tongue.

Single small foci of lymphocytes are present in the sections from rectus, diaphragm and quadriceps. They lie either in perimysial connective tissue or between muscle fibres. Atrophic and degenerative changes are present in most of the sections but are variable in degree. This atrophy is extreme in the quadriceps but patchy in distribution so that relatively normal fibres alternate with others less than 5 in width in which subsarcolemmal nuclei are condensed and striations persist. In the pectoral and rectus the changes are intermediate in degree whereas elsewhere they are slight.

Peripheral Nerve : Four consecutive blocks were taken from the right femoral nerve and nine from the right brachial plexus. Apart from a tiny collection of lymphocytes around a vessel in perineural fat in one section from each nerve, no abnormality is seen.

Synovial Tissue : A block was taken from the right knee (lateral compartment) and the right shoulder.

In the knee the membrane is of fibrous type without villi and having a lining of synovial cells never more than two or three layers deep and often attenuated so that it is only one layer thick with cells at some distance apart. The immediately subjacent layer is thin, consisting of loose cellular and vascular fibrous tissue with abundant fibres and containing small numbers of lymphocytes. Beneath this again is a bbroader band of well-developed and less vascular fibrous tissue and between this and the capsule an even broader layer of fibro-fatty tissue rich in capillaries some of which are cuffed with a narrow zone of lymphocytes. The synovial membrane proper is thus thickened to 2 mm. The capsule is healthy.

In the shoulder, the membrane is again of fibrous type with villi and a well-developed synovial lining usually several layers thick. Isolated segments of this lining have undergone fibrinoid change. The subsynovial layer and core of the villi consists mainly of fine and moderately cellular collagenous tissue with many capillaries and sparse infiltration with lymphocytes. One large villous contains very cellular collagenous tissue with large, swollen round or polyhedral cells and fibres which are swollen and have become fused into a homogeneous mass. Parts of such areas show metaplasia to cartilage and bone.

Right/

Right Femoral Condyle : Articular cartilage is present only at the very edge of the articular surface as a thin piece which has lost its zonal arrangement and has many necrotic cells. As one approaches the surface, the cartilage gives way to an irregular layer of fibrous tissue which covers the whole articular surface including the large part where no cartilage is present. It is of varying cellularity, most of the cells being fibroblasts, contains numerous widely dilated capillaries and is oedematous. The surface is almost everywhere necrotic with a fibrinoid appearance. Frequent patches of metaplasia to cartilage are seen in the deeper parts of this tissue, particularly in the neighbourhood of trabeculae of the underlying bone.

There is no subchondral plate, its place being taken by irregular bone trabeculae running perpendicular to the joint surface. The frequent gaps between these trabeculae contain fibrous tissue similar to that lining the end of the bone and this infiltrates for short distances between the trabeculae. No osteoclasts are seen, but the irregular outline of the trabeculae with numerous lacunae suggests that they are being eroded. The cortical and cancellous bone of the shaft show extreme atrophy. The marrow is all fatty.

Pathological diagnosis :-

Rheumatoid arthritis affecting all peripheral joints, with secondary osteoarthritis of knees.
Healed rheumatic peri-, myo- and endocarditis with non-specific chronic inflammation of mitral valve.
Brown atrophy of myocardium.
Atheroma of aorta and its main branches and coronary arteries.
Pulmonary embolism.
Fatty degeneration of liver with active regeneration.
Cholelithiasis with hydrops of gall-bladder.
Pancreatosis.
Benign nephrosclerosis.
Uterine fibroids.
Right ovarian cystadenoma.
Atrophy of skeletal muscle with occasional lymphorrhages.
(Parkinsonism).

Case 15.

M aged 26. Ref :- LIV/ 514.
RA of 13 years' duration affecting right shoulder, left elbow, right wrist and left ankle. Tissue obtained at excision of head of left radius. (Fig. 14).

Case 16.

F /

Case 16.

F aged 85. Ref :- PM. 34/49
RA of unknown duration affecting hands and knees. Death from strangulated femoral hernia of a week's duration. Synovial tissue obtained from knee.

Case 17.

David S. aged 54.
Admitted 7.3.49 to Northern General Hospital, Ward 2.
Died 7.3.49.
Autopsy 8.3.49 by Dr. K. Rhaney.
Abstract of Case Notes :- Said to have had rheumatic fever in 1916 but within a year the diagnosis was changed to rheumatoid arthritis. Most joints affected at some time since then with periodic exacerbations. The most recent exacerbation occurred three months ago and was treated with gold. Slight skin reaction two weeks before admission was controlled by B.A.L.
Fevered and unwell. Six days ago became gradually jaundiced and vomited a little. Began to have a severe haemoptysis 3 a.m. on 6.3.49. which persisted up to death. An attempt was made to transfuse the patient, but he had a sudden severe haemorrhage and was asphyxiated.

Macroscopic findings :-

The body was that of a middle aged man of average nutrition and good muscular development. He was intensely jaundiced. There were numerous petechiae in the skin, particularly of the lower part of the arms and legs and massive purpura had developed on the chest. No lymph glands were palpable and there was no oedema. There were no joint changes to suggest rheumatoid arthritis.
Head : Dura : Venous sinuses : were healthy.
Brain : was removed intact for neuropathological examination. It weighed 1460 G.
Mouth, Pharynx : contained fresh blood.
Neck and Thorax : Thyroid : N.A.D.
Larynx, trachea, main bronchi : contained a large quantity of frothy fresh blood and the mucous membrane was stippled with petechial haemorrhages which were most numerous in the main bronchi.
Pleural sacs : There was extensive fibrinous pleurisy over the lateral aspect of the right upper and middle lobes and also over the upper part of the lower lobe, and in the interlobar fissures. This sac contained approximately 20 cc. of very heavily bile stained fluid. There was widespread fibrinous exudate over the upper surface of the right leaf of the diaphragm which was dark reddish blue in colour. Left sac showed acute fibrinous pleurisy over the lateral and lower part of the upper lobe. There was approximately 30 cc. of bloody, bile-stained fluid./

fluid.

Lungs : were voluminous and very heavy. Right lung weighed 1270 G., Left lung 860 G. In the right lung there was massive haemorrhagic consolidation affecting the greater part of all lobes leaving some aerated tissue at the apex and along the anterior border, with small areas elsewhere. On the lateral aspect there were numerous large projecting emphysematous bullae, some of which were probably of fairly acute onset. In the left lung there was a massive area of haemorrhage in the upper lobe beneath the patch of pleurisy. Elsewhere the tissue was somewhat congested and oedematous. The cut surface of all the haemorrhagic areas was rather dry, but there was a lot of fluid blood in the bronchi. The affected areas were either dark red or black in colour.

Pericardial sac : showed numerous petechial haemorrhages on both inner and outer surfaces, and haemorrhages were present beneath the epicardium. It contained a normal quantity of heavily bile stained fluid.

Coronary vessels : showed severe atheroma with calcification and marked narrowing.

Heart : Was moderately enlarged. Right ventricle and tricuspid ring were slightly dilated. Left auricle showed numerous petechiae beneath the endocardium. Mitral cusps were slightly thickened and the chordae were also thicker than usual, but there was no stenosis or incompetence. Left ventricle showed slight hypertrophy and moderate dilatation. There were numerous sub-endocardial petechiae, especially over the inter-ventricular septum. Near the apex there was considerable fibrous scarring of the muscle, particularly beneath the endocardium. Aortic cusps showed slight atheroma. There was considerable lipoid deposition in the aorta. The patches had a fan-shaped distribution. In the arch some of the patches were larger and showed ulceration.

Coronaries - marked atheroma.

Oesophagus : contained a small amount of altered blood.

Abdomen : Peritoneal Sac : was healthy. There were numerous small haemorrhages in the mesentery, in the retroperitoneal tissues and in the coronary ligament.

Stomach : was filled with a large quantity of partially altered blood and numerous petechial haemorrhages in the mucous membrane, the largest being ½ cm. in diameter.

Duodenum : showed slight irregular congestion and possible haemorrhage.

Small Intestine : contained bile, partially digested food, while the caeces in the colon were black and also stained with blood. There were numerous petechiae in both caecum and colonic mucous membrane.

Spleen : was enlarged to approximately 3 times the normal size. It weighed 450 G. It was extremely/

extremely soft and on section the appearance was that of an acute infective splenic reaction.

Liver : was considerably enlarged, weighing 1850 G. It was rather flabby especially the upper part of both lobes. The parenchyma was deeply bile-stained and in the softer areas there was intense congestion of the central parts of the lobules, which was more striking than elsewhere. It was not possible to detect necrosis and there was no evidence of previous damage.

Gall bladder : contained rather viscid bile (approximately 10 cc.) and greyish mucoid exudate. The biliary passages were devoid of bile and showed no obvious evidence of obstruction.

Pancreas ; Adrenal glands : showed no macroscopic abnormality.

Kidneys : were considerably swollen. The capsule stripped without difficulty. The cortex was rather firm and homogeneous, brown in colour, and poorly differentiated from the medulla. There was slight swelling of the cortex, but no features to suggest a distal nephrosis. Urinary passages merely showed bile staining.

Mid-femoral marrow : showed areas of reactive haemopoietic tissue alternating with areas of deeply bile stained fat.

Sternum marrow : was homogeneous and reddish brown.

Various muscles and nerves were removed for histological examination. The only abnormal feature was the presence of slight haemorrhage beneath the sheath of the right rectus, but this did not appear to infiltrate into the muscle. The left elbow joint was removed intact for subsequent examination.

Microscopic findings :-

Liver : Although there is some variation in the degree to which individual lobules are damaged, there is no appreciable difference between the picture in the two lobes.

Each lobule shows considerable loss of cells, with some dissociation of the liver cell columns, although there is virtually no collapse of the reticulin fibres. The remaining cells are loosely arranged as if the destroyed cells had been situated in all three zones of the lobules, although marked centrilobular congestion may indicate that more cells were killed in the central zone than elsewhere. Of the remaining cells, the majority show various degenerative changes, but it is difficult in many individual cases to decide whether or not the changes are due to cell death or that they represent a temporary disturbance. Most of the cells have a coarsely granular cytoplasm and are often swollen. Many contain fat vacuoles, which are more numerous and larger in the central cells. Many cells have swollen nuclei, and karyolysis is frequent. In some cases the cells have lost their nuclei,/

nuclei, while a few are multinucleated. The only cellular response to the death of liver cells is some lymphocytic infiltration of the portal tracts, with occasionally a few cells in the periphery of the lobules. There is no bile duct proliferation, and no fibrosis. Kupffer cells are swollen and contain coarsely granular masses of golden pigment, presumably released from dead cells for some cytoplasmic remains contain similar pigment.

Gall bladder : The wall shows a mild round cell infiltration, but the content of the sac contains many polymorphs as well as mononuclear cells and erythrocytes.

Lungs show confluent and extensive consolidation, which is the result of massive haemorrhage. There is an early inflammatory exudate in the haemorrhagic areas. Blood fills the larger bronchi as well as the air spaces.

Kidney : Some arteriolo- and arteriosclerosis with patchy fibrosis and atrophy. No evidence of a distal nephrosis.

Spleen. Some of the Malpighian bodies are enlarged. They show central hyperplasia of histiocytes with some necrosis. Their margins are ill-defined as lymphocytes appear to be diffusing into the pulp which is congested, and contains a slight excess of plasma cells.

Pancreas : Small interstitial infiltration of lymphocytes. No lesions of the parenchyma.

Oesophagus : Mild round cells infiltration of the mucous membrane, but no ulceration.

Mid-femoral marrow : shows mainly myeloid hyperplasia, but few mature polymorphs are present, most of the cells being myelocytes.

Addendum to Macroscopic Report (by Dr. Cruickshank) : Left Elbow : There is marked generalised villous hyperplasia of the synovial membrane with haemorrhage into the joint. The cartilage is eroded in many places and covered with granulation tissue, especially over the posterior surface of the capitulum and over the ulnar articular surface, the largest erosion being 2.3 mm. in diameter. Fairly marked osteophyte formation is seen around the olecranon and both condyles of the humerus.

Extra Microscopic Report : Heart (Figs. 222-225) : Blocks were taken from right auricle, tricuspid valve with adjacent auricle and ventricle, left auricle, mitral valve with adjacent auricle and ventricle, anterior cusp of mitral valve, interventricular septum and anterior papillary muscle. Sections from the two blocks of auricle show no significant lesions, but in those from the blocks which include auricle, ventricle and valve, several interesting changes are seen. A main right coronary artery and one of its branches show advanced atheroma with considerable narrowing of their lumina and extensive calcification in the wall of one of them. Similar changes, though less advanced, occur in some/

some of the smaller vessels. Other smaller vessels show a completely different lesion - a subacute arteritis with narrowing of the lumen due to cellular fibrous tissue in the intima, thickening of the media with similar tissue plus round cell infiltration, and marked round-cell infiltration of the adventitia. No recent thrombosis is seen, but in one vessel a large piece of homogeneous hyaline material immediately beneath the endothelium, suggests previous thrombosis with recanalisation. In some of these vessels no internal elastic lamina is visible but in others it is seen, attenuated but apparently intact. No necrosis of any elements in the vessel walls is seen ; polymorphs are absent.

The myocardium of the ventricles is healthy except in the block taken from the area where fibrosis was seen at autopsy. Here atheroma affects smaller arteries, and there is widespread fibrosis. In the inner part of the wall there is much more fibrous tissue than muscle and it is dense, acellular and mostly avascular. There are several large veins near the surface, from some of which haemorrhage has occurred. Further out the fibrous tissue becomes less in amount (gradually), and in the outer half it consists of scattered small discrete areas, quite irregular in distribution and not related to septal vessels. As in the larger areas there is no evidence of muscle necrosis. Similar patchy fibrosis is seen in the anterior papillary muscle.

The valves show swelling and hyaline change of collagen fibres, most marked in the mitral where, in two places, they are fused into dense hyaline masses. There is no evidence of previous valvulitis in either valve.

Skeletal Muscles (Figs. 160, 165, 166) : Blocks were taken from tongue, left and right rectus abdominis, pectoralis major, diaphragm and left biceps brachii. A large area of recent haemorrhage with early organisation, is present in the right rectus and in pectoralis major. Three medium sized perimysial arteries show changes of the same type as those described in the heart, viz : uniform infiltration of the adventitia with round cells and slight eccentric intimal fibrosis. In other sections occasional small collections of lymphocytes are seen, either between muscle fibres or in perimysial tissue, with perhaps two exceptions they are too small to be called definite foci.

Degenerative changes are minimal.

Synovial Tissue : Sections from the left elbow show areolar type membrane with marked villous hyperplasia, the villi being lined by one or two layers of synovial cells. The villi contain numerous swollen, eosinophilic collagen fibres, but no evidence of fibrinoid change is seen. Lymphocytes, plasma cells and histiocytes occur in dense foci around vessels, or distributed irregularly throughout the villi. In the centre of the dense foci, there are occasional capillaries, and in the largest/

largest focus there is a central looser area of larger cells with much less dense nuclei and a very occasional mitotic figure, the appearances resembling a germinal centre. Occasional plasma cells have eosinophilic cytoplasm, but no Russell bodies. Haemorrhage is less marked than naked-eye examination suggested and is confined in the non-villous parts of the membrane. The villi do show evidence of old haemorrhage in the form of extra- and intra-articular pigment.

Peripheral nerves (Fig. 198) : Single sections from five successive blocks of brachial plexus and femoral nerve were examined. Vascular lesions, very similar to those in the skeletal muscles, are seen in several of the sections. The discrete, dense round cell foci described by Freund et alii, are not seen.

Pathological diagnosis :-

Acute hepatitis.
Hepatic failure with multiple haemorrhages.
Rheumatoid arthritis.
Acute cholecystitis.
Subacute arteritis of heart, skeletal muscles and peripheral nerves.

Case 18.

M aged 49. Ref :- PM. 404/49.
RA of 2½ years' duration affecting shoulders, elbows, fingers and knees. Death from bilateral thalamic infarction. Synovial tissue obtained from right knee, right and left third proximal interphalangeal joints.

Case 19.

Herbert D. aged 56.
Admitted 17.1.50 to Eastern General Hospital, C flat.
Died 24.1.50.
Autopsy 24.1.50 by Dr.A.F.J. Maloney.
Abstract of Case Notes :- Rheumatoid arthritis for 10 years. Had 4 courses of Gold injections - last one 3 years ago. Was at work till June 1949. Was then in bed for 3 months with bronchitis - recovered from that and attended physiotherapy Dept. W.G.H. 3 times a week until 3 weeks ago when he caught a cold - shivery, vomited, headache. Cough became worse - a week later voice became husky, no pain. Also developed pleuritic type of pain in left chest.

On admission - very ill looking man, creps. in L. axilla, diminished air entry. Clubbing of fingers with vitiligo round nails of fingers, toes, L. nipple C.V.S. Mitral stenosis. C.N.S. Pupils reacted to light and accommodation. Ankle jerks absent. Plantars - bilaterally extensor. Haemopoietic : Small/

Small gland L. axilla, spleen ++, Liver edge palpable 2 fingers below costal margin in linea semilunaris. Hb 56%. W.B.C. 600/cu.mm. 1-2 polymorphs in 50 cells. Mainly lymphocytes. Bone marrow : Packed with cells - mainly myeloblasts, myelocytes. Received 1 pint of blood on 2nd. night of admission - and appeared to recover. Was also receiving 2 million units of Penicillin per day. This morning obviously extremely ill again - Cheyne-Stoking and collapsed.

Died 1.10 p.m.

Macroscopic findings :

The body was that of an anaemic middle aged male of average build and poorly nourished. There was oedema of both ankles and sacrum. The wrist joints, interphalangeal and metacarpal phalangeal joints showed the characteristic deformities of severe rheumatoid arthritis, but without much evidence of ankylosis. The knee and ankle joints were also probably affected though less severely. The fingers showed mild clubbing and vitiligo of the skin round the base of the nails. There was also vitiligo of the left nipple and toes.

Neither lividity nor rigidity was present as the autopsy was performed only 2 hours after death.

Serous Sacs : Pleural : Both sacs contained a little straw coloured fluid. The left sac was almost completely obliterated by dense fibrous adhesions. These were most marked over the lateral surface of the lung where parietal and visceral layers were fused together to form a plaque of scar tissue 0.5cm. thick at its centre and gradually becoming thinner towards its periphery. The plaque was firmly adherent to the periosteum of the ribs and to the underlying lung over which it formed a thick shell. This scar tissue was white in colour, homogeneous and exceedingly tough resembling in places tumour tissue.

In the right sac fibrous adhesions were present throughout but nowhere were they as dense as in the left.

Pericardial sac contained an excess of serous transudate. The serosa was healthy.

Peritoneal sac : N.A.D.

Reticulo-Endothelial System : The spleen was greatly enlarged and weighed 950 gms. but it retained its usual shape. There was a mild acute perisplenitis over the upper half of the organ, though elsewhere the capsule which was tightly stretched was smooth and glistening. On section the pulp was quite soft, reddish brown in colour but presented no striking abnormalities.

Lymph glands : The hilar glands were slightly enlarged, but quite soft in consistence. Some were anthracotic and quite firm, others were soft, oedematous and on section appeared congested. None showed any obvious tumour infiltrations. Elsewhere the lymph glands showed no abnormalities.

Bone/

Bone marrow : the sternal marrow was very red, soft and appeared hyperplastic.

Marrow from mid shaft of femur was non reactive and showed small areas of apparent gelatinous degeneration.

Respiratory System : Larynx, trachea and bronchi : their mucosa was exceedingly pale, and they were filled with copious white mucopus.

Lungs : Left : the lower third of the upper and the upper half of the lower lobes were completely consolidated and exceedingly firm in consistence. The interlobar fissures were obliterated by thick fibrous adhesions. Section showed the consolidated portions of lung to be slate grey in colour stippled with minute focal areas of carbon pigmentation and though the appearances resembled those of " grey hepatisation ", the firmness of the lung parenchyma in these areas and the increase in interstitial fibrous tissue which was also noted suggested rather an organising pneumonia. The remainder of the lung was congested and oedematous.

In the upper and outer part of the right lung a large rounded area of consolidation some 4 cm. in diameter was palpable. This, on section, showed generally an appearance similar to those areas of consolidation described in the left lung, but in addition one or two small foci of suppurative softening were seen in the centre of which abscess cavities were appearing. These were probably related to small bronchi. The remainder of the lung was oedematous. The interlobar fissures were obliterated.

Cardio-vascular System : The Heart, which was enlarged, weighed 450 gm. and was globular in shape. There was moderate left ventricular hypertrophy without dilatation, and well marked hypertrophy and slight dilatation of the right ventricle. Both auricles were slightly hypertrophied and dilated. The myocardium was firm in consistence and reddish brown in colour. In the left ventricle, upon the posterior wall, in the tips of the papillary muscles and on the interventricular septum were small focal areas of fibrous scarring which could be clearly seen through the endocardium. On section those in the walls of the ventricle had a plaque like appearance. The largest, which measured 4 x 3 mm. and was almost 3 mm. thick, lay upon the interventricular septum. The tip of one papillary muscle was practically completely replaced by scar tissue. In the other chamber the myocardium appeared healthy as did the endocardium. There was a well marked rheumatic mitral stenosis. The valve barely admitted 1 finger and the cusps were grossly and irregularly thickened and partially fused to one another at their margins. Both cusps also showed patchy areas of calcification with superficial ulceration of the endothelium upon the proximal surface of the cusp and terminal platelet thrombi deposition. The chordae were thickened and shrunken. The aortic valve cusps also showed a little irregular fibrous thickening/

thickening of rheumatic origin but there appeared to be neither stenosis or incompetence. Two small terminal platelet vegetations were seen upon the surface of the cusps. All other valves were healthy.

The coronary arteries and aorta showed minimal atheromatous changes in keeping with the patient's age.

Alimentary System : Mouth, pharynx, oesophagus : N.A.D.

Stomach : N.A.D.

Duodenum : A small area of doubtful radiate scarring was seen on the posterior wall of the 1st. part suggestive of a healed doudenal ulcer.

Small intestine : N.A.D.

Large intestine was normal except for mild diverticulosis of the pelvic colon.

The liver weighed 2,150 gms. The capsule was covered by a scanty fibrinous exudate upon the anterior surface of the right lobe. Elsewhere it seemed healthy. Section showed no striking abnormalities.

Gall bladder and bile ducts : N.A.D.

Pancreas : N.A.D.

Urogenital System : Kidneys appeared normal macroscopically.

Renal pelves and ureters : N.A.D.

Bladder was distended with clear yellow urine.

Genitalia : N.A.D.

Endocrine System : Thyroid, suprarenal and pituitary : N.A.D.

Central Nervous System : Calvarium, dura and sinuses : N.A.D.

Brain and cord were sent to Neuro-Pathology dept. for further examination.

Microscopical findings :

Lungs : sections from the areas of consolidation noted in both lungs show the presence of an organising pneumonia occurring in some places in collapsed lung tissue. Where inflammatory exudate still persists it is found to consist largely of fibrin with a variable number of histiocytes but for the most part this exudate has been replaced or is in the process of being replaced by cellular fibrous tissue which fills up the alveolar spaces and extends into the lumina of the smaller bronchi and bronchioles. The alveolar walls likewise show fibrous thickening and especially in those areas which are collapsed there is commencing septal cell proliferation. The small cavities shown in the consolidated portion of the right lung appear to have originated in bronchi. They appear as chronic abscesses filled with necrotic purulent debris and lined by a thick layer of chronic granulation tissue heavily infiltrated with lymphocytes and plasma cells.

The pleura overlying the consolidated lung is considerably thickened by a layer of oedematous cellular/

cellular active granulation tissue in which a little fibrinous exudate may still be recognisable.

There is no evidence of tuberculosis or of tumour.

In other parts of the lungs there is some degree of perivascular, peribronchial and interstitial fibrosis. There is moderate emphysema.

Lymph glands (Hilar) : there is no evidence of leukemic infiltration. The changes present indicate drainage of a septic focus - the sinuses are distended and contain lymphocytes, plasma cells and histiocytes ; plasma cells and histiocytes are also present in large numbers in the pulp.

Spleen : there is no leukaemic infiltration. The pulp is congested and contains many plasma cells. Iron laden histiocytes are present in some places. The appearances resemble those seen in " Septic spleen."

Liver : the normal lobular pattern is present and the portal tracts show no abnormalities. There is some terminal centri-lobular congestion.

Bone marrow : from mid shaft of femur is entirely non-reactive.

Heart : The mitral valve shows well marked fibrous thickening which for the most part is composed of dense collagenous tissue. The appearances are those of an old healed rheumatic lesion. In addition, however, small platelet thrombi are adherent to the auricular surface of the cusp. The underlying portion of the cusp shows no reaction to their presence and they are obviously terminal in origin.

Addendum to Microscopic Report, by Dr. Cruickshank:

Heart : (Figs. 204, 206, 208). Blocks were taken from the right auricle, right ventricle, left auricle, posterior cusp of mitral valve with adjacent auricle and ventricle (2), free part of posterior cusp of mitral valve, posterior papillary muscle and two patches of left ventricle showing subendocardial fibrosis.

A single tiny patchy of fibrosis of the epicardium is present in the section from right ventricle. Early atheromatous changes are seen in several coronary arteries in the subepicardial fat. A great deal of fibrosis has occurred in the myocardium, much of it being diffuse. This is seen in the right auricle where the fibrous tissue forms a core for the trabeculae carnae and in most of the sections of left ventricle where the appearances are those of coronary ischaemia or healed infarction. Near the mitral valve, however, much of the fibrosis in the ventricular muscle is in and around septa and sometimes there is a definite laminated arrangement of collagen fibres around vessels. In the mural endocardium, the only abnormality seen is a tiny patch of fibrosis in the left auricle just above the mitral valve. The thickening of the mitral valve is due mainly to well-developed fibrous tissue in which capillaries and/

and arterioles, the latter with thick walls, run almost to the free edge. The only cells other than fibroblasts are scattered lymphocytes. Patches of calcification without reaction and deposits of haemosiderin are also seen. In one section of the valve, there is a patch of structureless eosinophilic material on the auricular edge which is continuous at one point with swollen collagen fibres in the cusp whereas elsewhere it is separated from the cusp proper by a strand of eosinophilic material in the plane of the valve surface.

These findings confirm the naked-eye description of healed rheumatic endocarditis of the mitral valve. The lesion on the edge of the valve is probably a healed vegetation. The myocardial lesions are evidence both of healed rheumatic myocarditis and of myocardial ischaemia from coronary arterial disease.

Skeletal Muscle : Examination of single sections from two blocks of quadriceps and one of popliteus show no definite lymphocytic foci. Slight generalised atrophy is seen with a relative increase in subsarcolemnal nuclei. Some fibres are swollen, have lost their striations and are deeply eosinophilic : here and there such fibres are fragmented and are undergoing phagocytosis by macrophages.

Synovial Tissue (Fig. 15). Two blocks were taken from the synovial membrane, one from the medial meniscus of the knee. The membrane is lined by up to 7 layers of cells and in one section there are many rudimentary villi. Occasional small patches of fibrinoid change are seen in the surface layer and a single large villous which lies separate from the surface consists almost entirely of homogeneous or granular pink material which stains bright red with Masson's stain and contains moderate numbers of pyknotic nuclei and some haemosiderin. Along the side facing the membrane proper this villus is lined by a synovial layer. Beneath the surface of the membrane proper there is focal infiltration with lymphocytes and plasma cells, the foci being spindle-shaped and frequently containing granules of haemosiderin. The meniscus is frayed at the tip and at its root are many fine villi showing the features already described.

The appearances are compatible with, though not diagnostic of rheumatoid arthritis.

Pathological diagnosis :-

Agranulocytosis.
Rheumatoid arthritis (" Felty's Syndrome").
Rheumatic endocarditis - Aortic and mitral valves : mitral stenosis.
Organising pneumonia.
Fibrous pleurisy.
Splenomegaly.
Perisplenitis and perihepatitis.
Diverticulosis.
Healed duodenal ulcer.

Case/

Case 20.

Janet M. aged 38. Ref :- LIII/2354.
Operation 23.11.49 in Royal Infirmary, Ward 2.
History of pain and stiffness in left knee for some weeks : palpable small mass at outer side of patella. Xray showed a very faint shadow suggesting a cartilaginous loose body. At operation a fibrous nodule was found attached to the lateral border of the patella by a pedicle. Subsequent involvement of metacarpophalangeal joints.

Case 21.

F aged 70. Ref :- MHA 3467.
RA of one years' duration affecting hands, knees and ankles. Death from bronchitis and bronchopneumonia superimposed on renal amyloidosis and healed pyelonephritis : also general thrombotic tendency. Synovial tissue obtained from left knee (Fig. 8).

Case 22.

M aged 39. Ref :- PM. 632/46.
RA of 12 years' duration affecting hands, knees, hips, feet, right wrist, neck and jaw. Death from colchicine poisoning. Synovial tissue obtained from right knee and first left proximal interphalangeal joint. This case was reported in detail by Macleod and Phillips (1947).

Case 23.

F aged 57. Ref :- LIII/2239 and LIV/ 488.
RA of 8 years' duration affecting wrists, hands, left shoulder and knees. Tissue obtained at synovectomy of right and left knees respectively (Figs. 5, 6, 12). Subsequent involvement of right elbow.

Case 24.

F aged 61. Ref :- P.M. 287/ 50.
RA of 4 years' duration affecting wrists, hands, and feet. Death from pulmonary embolism : also carcinoma of right ovary with extensive peritoneal and pelvic spread. Synovial tissue obtained from right knee.

Case 25.

James P. aged 48.
Admitted 27.5.50 to Royal Infirmary, Ward 31 (Case 487).
Died 29.5.50.
Autopsy 31.5.50 by the writer (PM. 340/50).
Abstract of Case Notes :- Miner prior to joining/

joining army. Discharged from Army A.1. Returned to his old work but injured a knee and was given light work as platelayer. About 18 months ago had swelling and pain in joints. 5 weeks ago began to be very tired and breathless. On admission was grey and cyanosed. Liver enlarged 3 fingers. Heart sounds faint but there was a systolic and localised mitral diastolic at apex. Treatment with coramine, digoxin and oxygen had little effect and pulse became weaker until death.

Macroscopic findings :-

The body was that of a well developed and rather stout, middle aged man, showing considerable fullness of the abdomen. Both hands showed typical deformities of well developed rheumatoid arthritis with ulnar deviation at the metacarpo-phalangeal joints, some spindling of the interphalangeal joints, particularly the 3rd. left proximal one, hyper-extension of these joints and atrophy of the skin of the fingers.

Examination of the other joints did not show any abnormality. No subcutaneous nodules were seen.

The right shoulder was dissected and the only abnormality discovered was a localised area of thickening and congestion of the synovial membrane in the upper posterior part of the joint.

Both knees were examined and showed more or less similar and symmetrical changes. These were mainly osteo-arthritic, indicated by some fibrillation and loss of cartilage on the patellar facet of the femur. A lesser degree of this change was seen on both patellae. In both joints the synovial membrane was congested and somewhat thickened with small villous projections here and there, but there was no evidence of a "pannus", and apart from the changes described, the cartilage appeared completely healthy. Excessive quantities of viscous, lemon-yellow fluid were present in each joint.

The metacarpo-phalangeal and proximal inter-phalangeal joints of the 3rd. left finger were removed for microscopic examination.

Serous Cavities : The pericardial cavity was completely obliterated by adhesions, most of which were dense and fibrous, though here and there the two layers could be fairly readily separated and the adhesions, though not fibrinous, appeared more recent.

The pleural cavities were all but obliterated by similar dense fibrous adhesions.

In the peritoneal cavity there was a small effusion of note more than 100 cc. of serous fluid, present mainly in the lower part of the cavity, whereas in the upper part dense adhesions were again present, binding the whole of the anterior, upper and posterior surfaces of the liver to the diaphragm.

Cardio-Vascular System : Heart - 720 G. (Figs. 209-211). The heart was moderately enlarged, this being due to dilatation and hypertrophy of the right side/

side and to some dilatation of the left ventricle. The muscle was everywhere paler than normal, but did not show any other abnormality. The mural endocardium was healthy. The tricuspid valve admitted 5 fingers with a good deal to spare and on the anterior and septal cusps of the valve small, warty, reddish vegetations were present on the auricular surface along the line of closure, but despite this the cusps themselves die not appear to be thickened. The chordae tendineae were healthy. Similar changes, but much more marked were seen affecting the mitral valve, both cusps of which were short and thickened, but not calcified, so that there was no stenosis and indeed 5 fingers could be inserted through the opening. The vegetations, most of which were less than 1 mm. in diameter, lay along the line of closure on the auricular surface. Some of them, slightly larger - one in particular was nearly 4 mm. in diameter - lay on the auricular surface in the angle between the anterior and posterior cusps. Apart from this isolated example, no spread had occurred to either the chordae tendineae or to the adjacent mural endocardium.

On the aortic valve a number of similar small, white vegetations were present along the line of closure of the cusps on the ventricular aspect. Here, there was very little thickening of the cusps themselves and no calcification, and the valve being competent to the crude water test. Coronary vessels were healthy.

The aorta showed practically no atheroma.

Respiratory System : Larynx, trachea and bronchi : The trachea and bronchi showed very considerable congestion of their mucous membrane and contain a small quantity of mucoid material.

Lungs : (Right 1130 gms. L 860 gms.) Both lungs were enlarged and contained a great deal of fluid. Apart from the adhesions' already mentioned external examination revealed a few fairly large nodules of firm consistence. On section the oedema was confirmed and there was also seen to be a considerable amount of congestion, the nodules being due to a superimposed bronchopneumonia.

Alimentary System : Both tonsils were slightly enlarged and on section contained a small quantity of purulent material and debris.

Pharynx, oesophagus, stomach and intestines were healthy.

Liver (1480 gms.) No examination of the external surface could be made on account of the dense fibrous adhesions. On section a very marked degree of chronic venous congestion was seen.

Gall bladder, biliary system and pancreas were healthy.

Urogenital System : Kidneys (R. 180 gms. L 160 gms.) : The kidneys were normal in size and shape, showing no abnormality on external examination. On section the cortex was normal in depth and rather pale, whereas the medulla showed fairly marked radial striation due to congestion.

Calyces/

Calyces, pelves, ureters, bladder and prostate were healthy.

Lymphatic and Haemopoietic System : Spleen (100 G.) The spleen was rather surprisingly small and was attached to the diaphragm by a few dense bands. No other abnormality was seen on external examination. On section early congestion was seen. No abnormality of the lymph nodes was seen anywhere in the body.

Bone Marrow : In the mid shaft of the femur (right) was entirely fatty.

Endocrine System : Pituitary and Suprarenals showed no abnormality on external examination.

Thyroid : Both lobes of the thyroid were considerably reduced in size and showed a marked degree of fibrosis of the parenchyma. Here and there small nodules of colloid-containing parenchyma were seen.

Central Nervous System : The brain was sectioned fresh but did not show any abnormality.

Microscopic findings :-

Autolytic changes mask the histological appearances in most organs.

Heart (Figs. 212 - 214). Blocks were taken from right auricle : right ventricle ; tricuspid valve and root, pulmonary valve, left auricle, mitral valve and root, posterior cusp of mitral valve, anterior wall of left ventricle, interventricular septum, posterior papillary muscle, aorta (2) and aortic valve(2).

Evidence of rheumatic carditis is seen in the form of

a) Aschoff bodies which are scattered in small numbers throughout the myocardium being most numerous in the right auricle near the tricuspid valve. All are small but show a well developed zone of Aschoff cells around central necrotic collagen. Other cells are scanty, being mainly small numbers of lymphocytes. No healing Aschoff bodies are seen.

b) Subacute or chronic valvulitis of all valves. This is most active in the aortic valve whereas in the others the inflammation is subsiding. Patches of necrotic hyaline material (" fibrinoid") are seen in tricuspid, mitral and aortic valves and are mostly within the valve substance rather than on its surface. Platelet vegetations are not seen, nor are there any Aschoff bodies in the valves.

c) Subacute arteritis mainly in the posterior papillary muscle.

d) Septal fibrosis sometimes perivascular is present in all sections of myocardium.

e) Vascular epicardial adhesions with patchy round cell infiltration but no Aschoff bodies.

Other features are patchy, loose, non-specific infiltration of septa with polymorphs, lymphocytes and occasional numbers of plasma cells and histiocytes and hypertrophy of muscle fibres in right auricle, right ventricle and left auricle.

Lungs/

Lungs : Two sections confirm the oedema and congestion. They show also organising exudate in a few alveoli and a good deal of intra-alveolar haemorrhage.

Liver : Very severe chronic venous congestion with marked atrophy and degeneration in the centre of the liver lobules.

Pancreas : N.A.D.

Kidney : Venous congestion in medulla and generalised toxic changes.

Spleen : Moderate congestion of pulp.

Pituitary : A single clump of squamoid cells is seen, not in the usual position around the stalk but in the fibrous capsule at the antero-superior pole of the gland. No other abnormality.

Thyroid : Well-marked involutionary changes are seen with fibrosis and lymphocytic infiltration. These tend to be patchy and a good deal of functional tissue remains.

Suprarenals : Moderate congestion in deeper cortex.

Skeletal Muscle : Blocks were taken from rectus, pectoral, diaphragm, psoas, quadriceps, deltoid, muscles of left hand and tongue. No significant lesions were seen.

Peripheral Nerve (Fig. 189): Three consecutive longitudinal blocks were taken from the right femoral nerve and the left brachial plexus. Small collections of lymphocytes are seen in the perimysial tissue or within the nerve fibre in one section from each nerve.

Synovial tissue : Only slight patchy changes are seen in a section from the right shoulder, namely, congestion, necrosis of the surface layer, oedema and perivascular lymphocytic infiltration. No proliferation of synovial tissue is seen. Similar but more marked features are present in sections from three different parts of the right knee with the addition of slight but definite increase of the number of villi and the patchy hyperplasia of the surface cells. No Aschoff bodies are seen.

Flexor tendons from left palm : The tendon sheaths show features similar to but slightly less than those in the shoulder, and the tendons themselves are healthy.

Joints :

a) 3rd. left metacarpo-phalangeal : synovial tissue is excessive and congested, but not inflamed. There has been destruction of cartilage towards the palmar aspect of both bones and replacement by dense fibrous tissue without adhesions.

b) 3rd. left proximal interphalangeal : Similar with superimposed early osteoarthritis.

c) right sacro-iliac : synovial tissue is present in only one of the three blocks - it is healthy. The cartilage shows degenerative changes of an osteo-arthritic nature and the underlying bone trabeculae are thickened.

d) Manubrio-sternal joint : Most of the joint has been replaced by cancellous bone with haemopoietic/

poietic marrow in its spaces. Islands of hyaline cartilage undergoing gradual replacement by bone are all that remain of the joint. These findings confirm those obtained on X-ray where there is bony ankylosis of all except the margin of the joint on either side.

Pathological diagnosis :-

Inactive rheumatoid arthritis with early osteoarthritis.
Subacute rheumatic carditis with pericardial adhesions, Aschoff bodies in myocardium and valvulitis of all valves.
Pleural and peritoneal adhesions.
Congestive cardiac failure.
Bronchopneumonia.

Case 26.

Mrs. Isobel R. aged 82.
Admitted 18.10.49 to Royal Infirmary, Ward 11 (Case 17869).
Died 23.10.49.
Autopsy 25.10.49 by Dr. C.C. Gardner.
Abstract of Case Notes :- Whilst going to W.C. at 5.30. in morning of 18.10.49 slipped and sustained fracture to base of neck of right femur. Rheumatoid arthritis for many years : Compression fracture of right forearm with resultant ankylosis - 70 years ago. : cholecystectomy 17 years ago : neck abscess drained 1947. Fibrillating with waterhammer pulse, double aortic and systolic mitral murmurs.
On 21.10.49 operative reduction with Smith-Peterson pin. Rallied for an hour in afternoon of 21.10.49 injection of 1/6 g. morphine at 4.30 p.m. 21.10.49 and never recovered consciousness.
History of auricular fibrillation and two previous cerebro-vascular accidents.

Macroscopic findings :-

Autopsy 18 hours after death. The body was that of a well nourished elderly female showing post mortem lividity and rigor mortis. The right elbow was fixed in 120° flexion. Both hands showed ulnar deviation at the wrists, slight subluxation at the metacarpo-phalangeal joints, enlargement of metacarpal heads, and Heberden nodes. There was a gross condition of pediculosis capitis. There was an old scar of the Kocher's right subcostal incision, and a recent wound of right thigh extending six inches downwards from greater trochanter.
Serous Sacs : Pericardial and peritoneal sacs N.A.D.
Pleural sacs : Left upper lobe of lung was adherent antero-laterally over an area of 5 cm. square by dense pleural adhesions to parietal pleura. There was/

was no free fluid in either sac.

Cardio-Vascular System : Heart : 480 gms. Enlarged to 1½ times normal size. The epicardium and subepicardial fat showed no abnormality. Myocardium was somewhat flabby but of normal colour and there were no infarcts or scars. Right auricle and ventricle were markedly dilated. Left auricle showed no abnormality. Left ventricle : was enlarged, and walls were hypertrophied to twice usual thickness. Pulmonary vessels : N.A.D.

Aorta : Showed increasing atheroma and tortuosity as it was traced inferiorly. The walls of common iliac arteries and lowest part of aorta were largely replaced by calcified atheromatous plaques.

Pulmonary trunk was free of thrombus.

In each femoral vein some thrombus was found, but was typical of post mortem formation.

Respiratory System : Larynx, trachea and bronchi were coated with frothy mucus decreasing in amount from below upwards.

Lungs : R 300 gms. L 380 gms. Visceral pleura : N.A.D. Shape and size were normal, except for failure to collapse of posterior parts of upper and especially lower lobes. Cut surfaces showed marked congestion and oedema of the dependent non-collapsed parts, but no consolidation could be detected.

Alimentary System : Edentulous. Mouth and pharynx : N.A.D.

Oesophagus : Mucous membrane was thickly coated with frothy mucus, probably from swallowed bronchial excretion.

Stomach, duodenum and intestines : N.A.D.

Liver : 1260 gms. Slightly enlarged, of normal shape, contour and peritoneal covering. Colour was redder than average. The cut surface showed mottling of early chronic venous congestion and some cloudy swelling.

Gall bladder : Had been removed. There was a few old peritoneal adhesions in this region.

Pancreas : N.A.D.

Spleen : 100 gms. Was small, but of normal shape and surface. Cut surface showed prominent Malpighian bodies and shiny appearance of commencing post mortem autolysis.

Urogenital System : Kidneys : R 80 gms. L 140 gms. Both markedly reduced in size. Capsules stripped with some difficulty revealing granular surfaces with whitish granules and red interspaces. In each there were several congenital cysts, containing clear fluid, situated in the cortex, varying in size from 1 to 3 cm. in diameter, and with smooth linings. None communicated with the renal pelvis. On section, the cortex was much reduced in depth, and coarsely mottled with grey-white patches ; it was poorly differentiated from medulla which showed similar changes to a less degree. There was some increase in peri-pelvic fat, but no hydronephrosis. Small branches of renal arteries could be seen to have thickened fibrotic walls.

Ureters/

Ureters and Bladder : N.A.D.
Uterus : Small, atrophic and with a mild degree of senile endometritis, at the fundal end of uterine cavity.
Ovaries : Small and atrophic.
Endocrines : Thyroid and suprarenal glands : N.A.D.
The right knee joint was opened : both tibial and femoral bone ends appeared broadened. There was some eburnation of patella and tibial articular surfaces. Menisci were represented only by peripheral fibrous rims. Almost complete rings of osteophytes surrounded femoral, patellar and tibial articular surfaces. Joint capsule was generally thickened. There was no increase in synovial fluid.

Microscopic findings :-

Heart : The cusps of the mitral valve were sectioned at intervals of 2-3 mm. revealing scanty nodular calcification of the ring. The chordae to the anterior cusp were thickened and slight stenosis of the valve was present. The aortic cusps were thickened but not calcified. Considerable atheromatous changes were found in all branches of the coronary arteries.
Blocks were taken from R. auricle, right ventricle (2), left auricle, mitral valve with adjacent auricle and ventricle, interventricular septum and anterior papillary muscle. Patchy fibrosis is present in all sections of ventricular muscle examined. It is often intimately mixed with muscle fibres and where focal is not of septal distribution. In most places the fibrous tissue is acellular but some foci in the papillary muscle contain numbers of slightly swollen fibroblasts and a few capillaries indicating more recent development. No signs of infarction are seen, but atheromatous changes, including calcification, affect many branches of the coronary arteries.
Skeletal Muscle : Blocks were taken from rectus abdominis, pectoralis major, diaphragm, quadriceps and psoas. No inflammatory foci are seen and degenerative changes are minimal.
Peripheral Nerves : (Fig. 197) Five successive longitudinal blocks were taken from a femoral nerve and two from a median nerve and single sections from each examined. In two sections of femoral nerve, loose focal collections of lymphocytes are seen within nerve bundles and in another there is an organising thrombus in a perineural artery.
Synovial tissue : Two blocks were taken from the synovial tissue of the right knee. One is of fibrous type with several small villi, the other adipose. Neither shows any hyperplasia of lining cells ; indeed attenuation is quite often seen. Deep to the surface region, acellular fibrous tissue is present in excessive amounts. Very occasional patches of fibrinoid change occur in this region, but inflammatory changes are minimal - scattered round/

round cells in the superficial parts of the synovial membrane and around small vessels in the capsule.

Flexor tendons of L. hand : The flexor tendons in the palm of the left hand were dissected, revealing no naked-eye abnormality. Sections, however, show that frequent collagen fibres are swollen and hyaline with fragmentation and pyknosis or karyorrhexis of nuclei. These hyaline or necrotic fragments are being absorbed by macrophages and there is scanty lymphocytic infiltration, the latter tending to be focal. Small numbers of capillaries are seen associated with the areas undergoing absorption. Bands of normal fibres alternate with bands of affected ones. The tendon sheaths are healthy.

Pathological diagnosis :-

Operative internal fixation of cervical fracture of right femur..
Hypertrophy of the left ventricle of the heart, and dilatation of the right ventricle.
Aortic atheroma.
Pulmonary congestion and oedema.
Venous congestion of the liver.
Arteriolosclerotic kidneys with congenital cysts.
Ankylosis of right elbow : osteoarthritis of right knee ; rheumatoid arthritis of both hands.
Pediculosis capitis.

Case 27.

F aged 82. Ref :- PM. 416/50
RA of many years' duration affecting many joints. Death from shock following operative reduction of fractured neck of femur. Synovial tissue obtained from right eblow, and knee, third left metacarpophalangeal and interphalangeal joints.

Case 28.

F aged 57. Ref :- MHA 3851.
RA of 21 years' duration affecting most limb joints. Death from extensive pulmonary tuberculosis and early bronchiectasis. Synovial tissue obtained from left knee and second right metacarpophalangeal joint.

Cases 29 - 34.

The sections in these six cases came from the collection of the late Dr. Ernst Freund.

Case 35.

F aged 54. Ref :- MHA 844.
RA of 10 years' duration affecting elbows, wrists/

wrists, hands, knees, feet and ankles. Death from pulmonary embolism. Synovial tissue obtained from knee.

Case 36.

F aged 54. Ref :- MHA 844.
RA of 3 months' duration affecting hands, knees and feet. Death from miliary tuberculosis and active pulmonary tuberculosis. Synovial tissue obtained from knee.

Case 37.

F aged 70. Ref :- LII/842.
RA affecting right knee for 3 years. Tissue obtained at arthrodesis.

Case 38.

M. Ref :- XXXIII/ 368.
RA affecting left knee for 3 years. Tissue obtained at arthrodesis (Fig. 10).

Case 39.

F aged 40. Ref :- LIV/ 2510.
RA of 9 years' duration affecting wrists, hands and L. elbow. Tissue obtained at arthrodesis of left elbow. (Figs. 3 & 7).

Case 40.

F Ref :- PM. 36/ 51.
RA of many years' duration affecting hands, wrists and knees. Death from cerebellar haemorrhage and purpura following chrysotherapy. Synovial tissue obtained from right knee and all joints of third left finger and from prepatellar bursae (Fig. 36).

Case 41.

M aged 62. Ref :- MHA 4168.
RA of 5 years' duration affecting shoulders, wrists, hands, knees and ankles. Death from acute cardiac failure superimposed on cor pulmonale and emphysema : also adenocarcinoma with extensive metastasis (primary site undiscovered). Synovial tissue obtained from right knee.

Case 42.

M aged 59. Ref :- MHA 4060.
RA of 20 years' duration affecting hands, knees and feet. Death from empyema complicating chronic bronchitis and early bronchiectasis. Synovial tissue obtained from left knee.

Case 43.

Robert/

Robert D. Aged 2½
Admitted 13.12.50 to Royal Hospital for Sick Children, Ward 7.
Died 11.5.51.
Autopsy 11.5.51, by Dr. A.E. Claireaux.
Abstract of Case notes :- Onset of pain, stiffness and swelling in left shoulder and neck at 20 months. Other shoulder, elbows, left knee, left foot and left hand involved in turn thereafter, with effusion in knee. No radiological evidence of bony damage. BSR 37, Wbc, 19000, Hb 78%. Some response to physiotherapy and to insulin. No history of rheumatic fever : heart normal. Developed symptoms of obstruction of small intestine: adhesions and peritonitis found. Died on the operating table.

Macroscopic findings :-

The body was that of a fairly well developed male infant aged 2½ years and weighing 25 lbs. 12 ozs. Post-mortem lividity was present over the posterior trunk and limbs. There was a surgical incision over the left anterior chest. The incision had been closed by sutures and was the site of an operation for cardiac massage. There was a linear incision closed by sutures in the right anterior abdominal wall. It was the site of an operation to relieve intestinal obstruction.

The wrist joints and knee joints were swollen. When the left wrist joint and the left knee joint were opened, yellow purulent fluid escaped. Specimens were taken for culture. The left knee joint showed a marked degree of synovitis. The synovial membrane was swollen and bathed in yellow fluid. The articular cartilage was remarkably healthy ; no destruction had occurred.

Head : Dura mater and pia-arachnoid were perfectly healthy. Falx and tentorium were intact. Brain was firm and on section no intra-cerebral lesion was found.

Neck and Thorax : Pharynx and oesophagus were healthy.

Thyroid and thymus glands showed no abnormality.

Cervical lymph nodes were very slightly enlarged. On section they had a homogeneous appearance.

Trachea and bronchi were healthy. There was some thick mucus in the major bronchi.

Pleura was dull. Numerous adhesions were present between the visceral and parietal pleura on both sides. No free fluid was present.

Lungs were poorly expanded. There were areas of collapse at the apex of the upper and lower lobes of both lungs. On section the lungs were found to be deeply congested and poorly aerated. There was no pneumonia.

Pericardium was dull and there were dense adhesions between the visceral and parietal pericardium. These adhesions were very strong for the two layers of pericardium could not be separated from one another./

another.

The myocardium of the right ventricle was rather flabby. The tricuspid and pulmonary valves had a normal appearance. The right atrium was healthy. Foramen ovale was closed. Endocardium of the left ventricle was healthy. Aortic valve was normal. Mitral valve was healthy.

Abdomen : Peritoneum was dull and fine flakes of fibrin were adherent to the peritoneal surface of the coils of intestine and lightly bound the coils to one another. The mesentery was rather oedematous and swollen. The mesenteric lymph nodes were moderately enlarged and had a fleshy appearance on section.

The appendix was buried in some oedematous tissue but was not inflamed.

Stomach was of expected size and contained a little mucus.

Duodenum was healthy. Jejunum showed a few patches of congestion. Ileum showed numerous patches of intense congestion and numerous small areas of acute ulceration were present and were more plentiful towards the lower end. These areas of ulceration had not affected the Peyer's patches which appeared to be healthy. The ulcerated areas were very superficial. They were intensely congested and some blood had oozed from their surface. Specimens were removed for bacteriological examination. The appearance was that of acute enteritis of unknown aetiology. The colon was healthy.

Liver was of expected size. Capsule was smooth. On section the organ had a normal appearance. Gall bladder was large and contained some dark green bile. Bile ducts were healthy.

Spleen was one and a half times the normal size. Capsule was smooth. On section the pulp was found to be rather soft.

Suprarenal glands and the pancreas were healthy.

Kidneys were of expected size. Capsule was smooth and stripped easily. On section the cortex and medulla were healthy. Ureters were slightly dilated. Bladder was healthy and contained a large quantity of clear yellow urine.

Bacteriological Report :- Effusion from left knee : Direct film - Very numerous polymorphs. A few large mononuclear cells. Occasional endothelial cells. No organisms. Culture - (aerobic) - No growth after 72 hours.

Effusion from left wrist : Direct film - Excess of polymorphs. A few large mononuclear cells and an occasional lymphocyte. No organisms. Culture - (aerobic) - No growth after 72 hours.

Contents of ileum :- Direct film - Red blood cells. Mononuclear cells. Very numerous polymorphs. No organisms found. Culture - Heavy growth of enterococci.

Peritoneal fluid and exudate from bowel :- No pathogenic organisms of the dysentery or enteric group isolated.

Microscopic/

Microscopic findings :-

Lungs : The pleura is healthy. The lungs are intensely congested and very oedematous. The bronchi are healthy and their epithelium is intact. Many contain acidophile oedema fluid and numerous polymorphonuclear leucocytes. In many areas there is severe consolidation andthe alveoli are packed with polymorphonuclear leucocytes and histiocytes. The appearance is that of a hypostatic pneumonia developing in very oedematous lungs.

Thyroid Gland : The acini are lined with cubical epithelium and are well filled with colloid.

Kidneys : The capsule is normal. The glomerular epithelium and capillary tufts have a normal appearance. The tubules show early post-mortem change.

Spleen : The capsule and trabeculae are normal. The pulp is cellular and the Malpighian bodies are well developed and have a normal appearance.

Heart : The myocardium is healthy. There is no evidense of acute rheumatism.

Liver : There is considerable venous congestion and the liver cells show early fatty changes affecting all zones of the lobules. The portal tracts have a normal appearance and the bile ducts were healthy.

Mesenteric Lymph Nodes : The capsule is normal. The germinal centres are large and show reticulum cell proliferation. There are numerous histiocytes on the sinusoids. The appearance is that of non-specific lymphadenitis.

Ileum : Sections from the ileum show non-specific superficial ulceration of the mucosa. The bowel is congested.

Pancreas : The acinar epithelium and islet tissue are healthy. The ducts and fibrous tissue stroma have a normal appearance.

Heart : Sections were examined from the right auricle, tricuspid valve and root, left auricle, mitral valve and root, interventricular septum, aortic valve and anterior cusp of mitral valve. Vascular pericardial adhesions and infiltration of the ventricular myocardium, with small foci of lymphocytes, polymorphs, plasma cells and histiocytes were the only abnormalities seen. No Aschoff bodies or valvulitis were present.

Left Knee (Fig. 16) : Five blocks were taken. Most of the synovial tissue showed slight thickening of the surface layer without villous hyperplasia. Deep to the surface there was oedema and congestion throughout. In places this was accompanied by infiltration with lymphocytes and plasma cells of both focal and diffuse distribution and a few proliferating fibroblasts, whereas elsewhere well-formed fibrous tissue predominated. Polymorphs and eosinophils were scattered through the more active areas. Similar tissue extended over the surface of the articular cartilage.

Right/

Right wrist : Synovial tissue was similar to the knee with a greater degree of destruction of articular cartilage.

Muscle : Blocks were taken from rectus abdominis, pectoralis major, diaphragm, psoas and quadriceps. Occasional small lymphorrhages were seen in diaphragm and psoas.

Nerve : Seven blocks were taken from brachial plexus and femoral nerve. No lesions were seen.

Pathological Diagnosis :-

Juvenile rheumatoid arthritis.
Adherent pericardium.
Old-standing pleural adhesions.
Very early fibrinous peritonitis and acute enteritis, with non-specific ulceration of ileum.
Hypostatic pneumonia.

Case 44.

F aged 74. Ref :- P.M. 317/ 51.
RA of 2 years' duration affecting hands and wrists. Death from pontine haemorrhage complicating severe benign nephrosclerosis. Synovial tissue obtained from right knee, third right metacarpophalangeal and proximal interphalangeal joints.

Case 45.

F aged 59. Ref :- LV/ 1232.
RA of 17 months' duration affecting shoulders, elbows, wrists, hips and knees. Tissue obtained at cup arthroplasty of right hip (Fig. 9).

Case 46.

M aged 62. Ref :- PM. 391/51.
RA of two years' duration affecting shoulders, elbows, wrists and hands. Death from cardiac failure and severe exfoliative dermatitis following chrysotherapy. Synovial tissue obtained from right knee and a proximal interphalangeal joint.

Case 47.

M aged 53. Ref :- MHA 4392.
RA of 5 years' duration affecting hands, feet, right shoulder and elbow, wrists and knees. Death from malignant tumour of ileum with very extensive metastasis. Synovial tissue obtained from right knee and third right metacarpophalangeal joint.

Case 48.

F aged 72. Ref :- MHA 3917.
RA of several years' duration (? 5) affecting hands/

hands and knees. Death from left ventricular failure complicating severe benign nephrosclerosis: also chronic mitral and aortic endocarditis. Synovial tissue obtained from a metacarpophalangeal and proximal interphalangeal joint.

Case 49.

F Ref :- LV/ 2384.
RA of 7 years' duration affecting shoulders, hands, knees and ankles. Tissue obtained at arthrodesis of left knee.

Case 50.

F aged 45. Ref :- MHB 724.
RA of 7 years' duration affecting hands, knees and feet. Tissue obtained at arthrodesis of left knee.

Case 51.

M aged 64. Ref :- XLI / 433.
RA of 10 years' duration affecting wrists, shoulders and right knee. Tissue obtained at arthrodesis of right knee.

Case 52.

M aged 59. Ref :- MHB 711.
RA of 3 years' duration affecting elbows, wrists, knees and ankles. Tissue obtained at arthrodesis of right knee.

Case 53.

F aged 60. Ref :- EHB 985.
RA of 15 years' duration affecting hands, wrists, knees, ankles and feet. Tissue obtained at arthrodesis of right knee.

Case 54.

M. Ref :- EHB 1038.
RA of 11 years' duration affecting all joints except ankles and feet. Tissue obtained at arthrodesis of right knee.

Case 55.

F aged 19. Ref :- EHB 989.
RA of three years' duration affecting right shoulder, wrists and knees. Tissue obtained at arthrodesis of left knee.

Case 56.

M aged 53. Ref :- EHB 579.
RA of 5 years' duration. Tissue obtained from/

from knee.

Case 57.

F aged 33. Ref :- EHB 988.
RA of 6 years' duration. Tissue obtained from knee.

Case 58.

M aged 32. Ref :- EHB 1242.
RA of 3 years' duration. Tissue obtained from knee.

Case 59.

F aged 66. Ref :- EHB 1597.
RA of 17 years' duration. Tissue obtained from left knee.

Case 60.

F aged 48. Ref :- MHB 2822.
RA with splenomegaly, lymphadenopathy, anaemia and leukopaenia (" Felty's Syndrome") of 10 years' duration. Hands, elbows, knees, wrists, shoulders affected. Bursae and nodules on both elbows. Tissue from wall of bursa on left elbow (Fig. 51).

Case 61.

Robert C. aged 66.
15.7.49. Specimens submitted for examination with diagnosis of ? fibroma of forearms of 6 years' duration (EHB 2710). No information given about arthritis but specimens reported as identical with subcutaneous nodules of rheumatoid arthritis (Dr. K. Rhaney) (Figs. 96 and 97).
20.12.50. Further specimen (EHB 3299) submitted following enquiries by the writer. This was described as " olecranon bursitis " of 10 years duration and was reported as subcutaneous nodules of rheumatoid arthritis in wall of bursa by the writer (Fig. 49).
31.1.51. Letter from clinician (Mr J.C.Milne, Bangour Hospital), to effect that Xrays of hands and wrists show advanced rheumatoid arthritis.

Case 62.

M aged 45. Ref :- MHB 4729 and 4915.
RA of three years' duration affecting elbows, hands, knees, ankles, feet and cervical spine. Also bronchiectasis and calcinosis circumscripta. Tissue obtained from bursa on left and right elbows, respectively (Fig. 50).

Case 63.

Christina/

Christina S. aged 37. Ref :- RCP 1244/47.
Tenosynovitis of wrist developed shortly before typical RA which affected wrists, hands, knees, cervical spine and feet. Tissue obtained from extensor tendon sheath of wrist (Fig. 55).

Case 64.

M aged 26. Ref :- XLV/ 358.
Swelling right ankle and tendon sheaths of wrist for several months. Tissue obtained from tendon sheaths. Subsequent involvement of joints of hands.

Case 65.

M aged 47. Ref :- MHB 8970.
RA of 4 years' duration affecting hands, ankles and right foot. Involvement of tendon sheaths on dorsum of wrist three years after onset of arthritis. Tissue obtained from tendon sheaths (Fig. 54).

Case 66.

M aged 43. Ref :- LIII/ 2579.
RA of three years' duration affecting hands, elbows, knees and feet. Multiple " ganglia " over metacarpophalangeal joints. One of these was sent for examination as a " cyst " with no information about the arthritis. This was suspected on histological examination of tendon sheath and a nodule of rheumatoid type by Prof. A.C.P. Campbell and confirmed by the writer on examination of the patient.

SECTION II.

All the cases used for this Section have been listed already under Section I. They were Cases 1, 4-10, 12, 13, 15, 16, 18, 19, 23-27, 37, 39-41, 43, 44, 49, 50 and 54. See Table XVIII, p. 87.

SECTION III.

The following cases listed under Section I were used for this Section also :- Cases 1, 2, 12, 18, 20, 33, 40, 48, 60-62 and 66.

Case 67.

F aged 68. Ref :- MHB 2487.
RA of 24 years' duration affecting all limbs joints. Nodule from right ulnar border.

Case 68.

F aged 64. Ref :- LI/ 1029.
RA of two years' duration affecting wrists, hands,

ankles/

ankles and feet. Nodule from right elbow region. The patient also had mitral stenosis.

Case 69.

F aged 50. Ref :- LI/ 1194.
RA of 10 years' duration affecting hands and knees. Nodules on dorsal aspect of right second and third fingers. Tissue from one of these (Figs. 81 and 82).

Case 70.

M aged 31. Ref :- MHB 2624.
Pain in shoulders for 9 months and in left knee and feet for 8 months. Gonorrhoea 10 years previously. On examination spindling of inter-phalangeal joints, oedema of hands and wrists. Nodule on extensor aspect right elbow. Diagnosed at first as subacute rheumatism and later as very early, acutely active rheumatoid arthritis (Fig.85).

Case 71.

F aged 59. Ref :- MHB 2703.
RA of 5 years' duration affecting shoulders, elbows, wrists, hands and ankles. Nodule over second right interphalangeal joint. The patient also had mitral stenosis.

Case 72.

M aged 55. Ref :- MHB 2849.
RA of 10 years' duration affecting elbows, hands, knees and left ankle. Nodules on both elbows, ulnar borders, over metacarpophalangeal and interphalangeal joints of most fingers, ischial tuberosities and feet. Also silicosis and emphysema. Nodule taken from ulnar border.

Case 73.

M aged 36. Ref :- MHB 2916.
RA of one years' duration causing stiffness of fingers but no other joint symptoms. Nodules over third right and both fifth proximal inter-phalangeal joints. Subsequent development of typical joint lesions in hands and knees. Nodule taken from third right finger.

Case 74.

M aged 24. Ref :- MHB 2968.
RA of 4 years' duration affecting shoulders, hands, knees and feet. Single nodule on each elbow. Tissue taken from left elbow. (Fig. 87).

Case 75.

F /

F aged 57. Ref :- MHB 2987.
RA of 3 years' duration affecting shoulders, wrists, hands, knees, ankles and feet. Two nodules over right ulna (Fig. 87).

Case 76.

F aged 48.
RA of 22 years' duration with nodule on forearm for 4 years (Figs. 78 and 80).

Case 77.

M aged 35. Ref :- MHB 3077.
RA of 18 months' duration affecting shoulders, wrists and hands. Nodules over each elbow. Four previous attacks of rheumatic fever resulting in mitral stenosis and incompetence and aortic incompetence.

Case 78.

M aged 40. Ref :- MHB 3142.
RA of 7 weeks' duration affecting shoulders, elbows, hands, ankles and feet. Nodule over left ulnar border.

Case 79.

F aged 55. Ref :- MHB 3292, 3457, 8842 (a).
RA of 5 years' duration affecting shoulders, elbows, hands, knees and feet. Nodules over elbows and left thumb, some of which have disappeared. Tissue obtained from nodules over each elbow (3292 and 3457) and 2½ years later from recurrence on right elbow (8842 (b)).

Case 80.

F aged 68. Ref :- MHB 3341, 3431.
RA of 9 years' duration affecting shoulders, wrists, hands and knees. Nodules over right elbow, left ulnar border and interphalangeal joints. Tissue taken from right ulnar border (MHB 3341, Fig. 103) and right elbow (MHB 3431, Fig. 94).

Case 81.

F aged 81. Ref :- MHB 3340, 4551 :MHA 4251.
RA of 3 years' duration affecting shoulders, wrists, hands and knees. Multiple nodules on scalp, knees, shins, ankles and left foot. Tissue taken from left knee (MHB 3340, Figs. 88-93, 95). Subsequent development of nodule over dorsal spine ten months later (MHB 4551). Death from bronchopneumonia two years later when chronic mitral endocarditis was discovered.

Case 82.

F/

F. Ref :- LII/ 1856.
Nodules from elbow region diagnosed as "fibrolipomata" had histological appearance of rheumatoid nodules. This was confirmed, the joints involved being hands, wrists and right knee : also prepatellar bursitis : duration 9 years.

Case 83.

M aged 61. Ref :- MHB 5012.
RA of 3 years' duration affecting shoulders, wrists, hands, knees, ankles and feet and lower spine. Bursae and nodules on extensor surfaces of elbows. Subcutaneous and cutaneous nodules on thumbs and right index finger. The cutaneous nodules were numerous and of short duration, many of them ulcerating and then healing. Also episcleritis. Tissue obtained from right thumb (Fig. 86).

Case 84.

F 53. Ref :- MHB 5112.
Severe RA affecting shoulders, wrists, hands, knees and feet. Nodules on elbows. Bilateral iritis. Tissue obtained from left elbow.

Case 85.

Nodule from collection of the late Dr. Ernst Freund.

Case 86.

F aged 67. Ref :- LIII/ 1045.
Swelling from left forearm diagnosed as " ? tophi, ganglia or lipomata " had histological appearance of rheumatoid nodules. This was confirmed, the joints involved being shoulders, wrists and hands : duration many years. Also hypertension with minor cerebral vascular accident.

Case 87.

F aged 50. Ref :- MHB 6066.
RA of 39 years' duration affecting elbows, wrists, hands, ankles and feet. Nodules on both elbows and left wrist. Tissue obtained from left elbow (Fig. 98).

Case 88.

F aged 50. Ref :- LIV/ 673.
Nodule from extensor surface of forearm diagnosed as " multiple xanthomatosis," had histological appearance of cholesterol-containing rheumatoid nodule. This was confirmed, the joints involved being the wrists and hands : nodules on both ulnar borders. Xanthomata of eyelids : splenomegaly.

Case/

Case 89.

F aged 64. Ref :- MHB 6065, 6120.
RA of 15 years' duration affecting shoulders, elbows, hands and knees. Nodules on both elbows. (Fig. 102) Also bronchiectasis.

Case 90.

Nodule sent by Dr. H.F. West, Sheffield.

Case 91.

M aged 45. Ref :- MHB 6460.
RA of 12 yeers' duration affecting shoulders, elbows, wrists, hands, knees and ankles. Nodules on both elbows - tissue from left side.

Case 92.

M aged 58. Ref :- MHB 6461.
RA of 20 years' duration affecting left shoulder, right elbow, wrists and hands. Nodule on right elbow.

Case 93.

M aged 39. Ref :- MHB 5993.
The details of this case are given in the text (p. 140) The writer is indebted to Drs. Philip S. Hench, E.G.L. Bywaters, J.P. Kulka and Douglas H. Collins for opinions about the section.

Case 94.

F aged 51. Ref :- MHB 6961.
RA of 10 years' duration affecting shoulders, elbows, wrists, hands, knees and ankles. Nodules on left elbow.

Case 96.

F aged 22. Ref :- JJV/ 1882.
Specimen submitted with diagnosis "bursa of elbow " and no information about arthritis had histological appearance of rheumatoid nodules with adventitious bursa formation. This was confirmed, the joints affected being hands and feet : duration 5 years.

Case 97.

M aged 40. Ref :- MHB 1855.
RA of four years' duration affecting shoulders, and wrists. Nodules on elbow and toes. Also psoriasis.

Case 98.

M/

M aged 64. Ref :- LIV / 2550.
Nodules submitted as " lipomata " of both forearms. Large one (7.5 x 5.5 x 3 cm.) on right side was a fibroma whereas smaller one on left side was a rheumatoid nodule (Figs. 83 and 100). Diagnosis confirmed, joints affected being elbows, wrists, hands, knees, ankles and cervical spine. Other nodules on left wrist and left ankle.

Case 99.

M aged 61. Ref :- LIV/ 2318.
Specimen submitted as a fibroma had histological appearance of rheumatoid nodule. This was confirmed, the joints affected being hands and feet : duration 10 years.

Case 100.

M aged 57. Ref :- LV/ 2243.
RA affecting wrists, hands and left knee. Nodule on right knee.

Case 101.

F aged 56. Ref :- PM. 624/51.
RA of 28 years' duration. Death from diabetic coma. Nodule found on elbow.

Case 102.

F aged 65. Ref :- SD 1181.
RA of 7 years' duration. Nodules on dorsum of fingers of both hands.

Case 103.

F aged 46. Ref :- SD 1358.
RA of unknown duration. Nodules on both elbows and knuckles. Tissue from knuckle.

Case 104.

F aged 12. Ref :- XLVII/ 637.
See text p. 140 and Fig. 104.

Case 105.

M aged 48. Ref :- MHB 6119.
See text p. 161 and Figs. 180, 181.

Case 106.

M aged 53. Ref :- MHB 6118.
See text p. 161 and F 128.

Case 107.

M aged 54. Ref :- MHA 2417.
See text p. 171 and Fig. 137.

Case/

Case 108.

F aged 13. Ref :- LI/ 387.
See text p. 165 and Fig. 132.

Case 109.

F aged 66. Ref :- XL/ 63.
See text p. 161 and Fig. 129.

SECTION IV.

The following cases which were used in this Section have been listed previously :-

Cases 1, 2, 4, 5, 7-10, 12-14, 16-19, 21, 24-28, and 43 - under Section I and Cases 70, 72-74, 77, 78 and 81 - under Section III.

The following living patients suffered from typical uncomplicated rheumatoid arthritis, one or more small blocks (indicated in brackets) being removed at biopsy by the writer from the muscle mentioned :-

Case	110	Ref :- MHB	2573	right deltoid	(2)
	113		2867	" "	(2)
	114		2985	right quadriceps	(1)
	116		3004	" "	(2)
	118		3005	" "	(1)
	119		3012	R. extensor wrist	(3)
	121		3056	" " "	(1)
	122		3078	L. " "	(2)
	123		3090	" " "	(2)
	124		3089	R. " "	(2)
	126		3109	" " "	(1)
	128		3122	" " "	(2)
	129		2966	left deltoid	(1)
	130		2967	R. extensor wrist	(1)
	132		3245	" " "	(1)
	133		3251	" " "	(1)
	134		3252	" " "	(1)
	135		3291	" " "	(1)
	137		3408	right deltoid	(1)
	138		3418	R. extensor wrist	(2)
	139		3417	" " "	(2)
	140		3433	" " "	(2)
	141		3432	" " "	(2)
	142		3447	" " "	(2)
	143		3287	" " "	(1)
	144		3286	right deltoid	(1)
	145		3461	R. extensor wrist	(2)
	147		3480	" " "	(2)
	148		3520	" " "	(2)
	149		3519	" " "	(2)
	150		3545	" " "	(2)
	151		3617	" " "	(2)
	152		3616	" " "	(2)
	153		3625	" " "	(2) Fig. 175
	154/				

Case 155	Ref :-	3653	right	extensor	wrist (2)
156		3652	"	"	" (1)
157		3684	"	"	" (2)
158		3683	"	"	" (2)
160		3710	"	"	" (2)
161		3790	"	"	" (2)
162		3789	"	"	" (1)
163		3795	"	"	" (2)
164		3794	"	"	" (2)
* 166		3846	"	"	" (2)
171		3917	"	"	" (1)

* Case of juvenile rheumatoid arthritis.

In the following living patients, the rheumatoid arthritis was complicated by one or more other conditions. Muscle tissue was obtained as above.

Case 111.

Ref:- MHB 2838 right quadriceps (1)
Other conditions :- recent syphilis and gonorrhoea.

Case 112.

Ref :- MHB 2850 right deltoid (1)
Other conditions :- mitral incompetence following rheumatic fever.

Case 115.

Ref :- MHB 2984 left deltoid (1)
Other conditions :- rheumatic fever 25 years previously.

Case 120.

Ref :- MHB 3013 left extensor wrist (2). Figs. 142 and 143.
Other condition :- duodenal ulcer.

Case 125.

Ref :- MHB 3110. right extensor wrist (1)
Other condition :- peptic ulcer.

Case 127.

Ref :- MHB 3121 right extensor wrist (2)
Other condition :- methaemoglobinuria.

Case 131.

Ref :- MHB 3246 right extensor wrist (1)
Other condition :- psoriasis.

Case 136.

Ref :- MHB 3409 right extensor wrist (2)

Other/

Other condition :- inactive pulmonary tuberculosis.

Case 146.

Ref :- MHB 3462 right extensor wrist (2)
Other conditions :- old rheumatic heart disease and chronic bronchitis.

Case 165.

Ref :- MHB 3818 right extensor wrist (2)
Other condition :- rheumatic fever 10 years previously.

Case 167.

Ref :- MHB 3970 right extensor wrist (2)
Other condition :- rheumatic fever 41 years previously.

Case 168.

Ref :- MHB 3990 right extensor wrist (2).
Other condition :- diabetes mellitus.

Case 169.

Ref :- MHB 3918 right extensor wrist (1)
Other conditions :- hypertension and congestive heart failure.

In four other cases, muscle was obtained at autopsy :-

Case 117.

M aged 71. Ref :- MHB 3003 : MHA 3219.
RA of 3 years' duration affecting elbows, hands, knees and ankles. Death from liver failure following viral hepatitis : carcinoids of small intestine : senile hyperplasia of prostate. Muscle tissue obtained from rectus abdominis, pectoralis major, diaphragm, psoas, quadriceps, deltoid and tongue. Biopsy taken previously from right extensor wrist.

Case 159.

M aged 60. Ref :- MHB 3711 : PM. 132/ 49.
RA of 8 years' duration affecting hands, wrists, left shoulder and right ankle. Death from acute liver necrosis due to viral hepatitis : acute pancreatic necrosis : carcinoid of ileum. Muscle tissue obtained from rectus abdominis, quadriceps, gastrocnemius and tongue. Biopsy taken previously from left extensor wrist.

Case 170.

F/

F aged 50. Ref :- MHA 3018.
RA of 16 years' duration affecting many joints. Death from extensive pulmonary tuberculosis : pericarditis. Muscle tissue obtained from rectus abdominis, pectoralis major, diaphragm, psoas, quadriceps and tongue (Figs. 147, 161).

Case 172.

F aged 75. Ref :- MHA 3031.
RA of 12 years' duration. Death following laparotomy for inoperable carcinoma of gall bladder with extensive metastasis. Muscle tissue obtained from diaphragm.

SECTION V.

All the cases used in this Section have been listed previously -

Cases 1, 2, 7-10, 12-14, 16-18, 22 and 24-28 - under Section I and Cases 117 and 172 - under Section IV.

SECTION VI.

The following cases which were used in this Section have been listed previously -

Cases 1, 2, 4, 7-10, 12-14, 16-19, 21, 22, 24-28, 35, 36, 40-44 and 46-48 - under Section I.
Cases 81, 101, and 107 - under Section III and
Cases 117, 159, 170 and 172 - under Section IV.

Other cases used in this section are listed below, along with the lesions other than rheumatoid arthritis found at autopsy.

Case 173	Ref :-	PM 155/43	Severe exfoliative dermatitis following chrysotherapy : Confluent bronchopneumonia.
174		382/40	Psoriasis : bilateral apical tuberculosis.
175		370/47	Mitral stenosis : congestive cardiac failure.
176		592/38	Pulmonary embolism following R. femoral phlebothrombosis.
177		175/38	Carcinoma of splenic flexure.
178		162/33	Congestive cardiac failure (no microscopic sections available).
179		50/29	Cirrhosis of liver :healed pyelonephritis (no micro. sections available).
180	EHA	489	Fracture of right femur : fat embolism in lung, brain, kidneys and heart. (no micro. section from heart).
181	MHA	3416	Purulent bronchitis and early bronchopneumonia.

(Case/

(Case of juvenile rheumatoid arthritis)

Case	Ref.	
182	MHA 1717	Bronchopneumonia
183	MHA 1347	Aplastic anaemia following chrysotherapy.
184	MHA 351	Chronic bronchitis : congestive cardiac failure.
185	MHA 215	Bilateral pyonephrosis and nephrolithiasis.
186	PM 357/38	Purpura and massive tubo-ovarian haemorrhage following chrysotherapy.
187	PM 178/47	Cerebellar haemorrhage following a fall : benign nephrosclerosis : mitral stenosis (no microscopic section from heart).
188	PM 304/43	Haemorrhage anaemia : duodenal ulcer
189	PM 134/43	Intestinal obstruction (retention of faeces):
190	PM 474/47	Hepatic and renal tubular necrosis following chrysotherapy
191	MHA 4075	Bilateral bronchopneumonia
192	MHA 4201	Bilateral bronchopneumonia
193	MHA 4104	Cystic disease of lungs: pneumonia following bronchography
194	MHA 4553	
195	PM 69/52	Carcinoma breast : phlebothrombosis axillary and femoral veins : pulmonary embolism : early renal and adrenal amyloidosis.

ANKYLOSING SPONDYLITIS.

SECTION I.

In the following cases, synovial tissue was obtained at arthroplasty or arthrodesis and in all except Case 202, the material was supplied by Mr. D.L. Savill, lately Assistant Orthopaedic Surgeon, Bridge of Earn Hospital.

Case 196.

F Involvement of sacro-iliac joints and hips : tissue taken from right hip.

Case 197.

See pp. 435 a and b.

Case 198.

M aged 46. Involvement of sacro-iliac joints, lumbar, thoracic and cervical spine, knees, ankles and/

Case 197.

John G., aged 39. Ankylosing spondylitis, began as pain and stiffness in the gluteal regions at the age of 27. When seen eight years later, the thoracic and lumbar spine were rigid and movement at the hips was limited. B.S.R was 80 mm. in one hour. Flexion deformity developed thereafter in both hips. Arthroplasty of the hips was carried out on the right side on 10.5.49 and on the left side on 7.6.49.

Head and Neck of Right Femur and Tissue from acetabulum : Naked-eye : A few tags of villous synovial membrane are adherent to the neck of the femur. The articular cartilage has only a few normal areas. Elsewhere it is pale, rough, thin and pitted. Several areas, including one around the fossa for the round ligament have only a very thin layer of translucent tissue overlying the bone which is deep red in colour. On section, the part of the head supero-lateral to the fossa consists of pale yellow material, and this tissue also spreads round towards the lower edge of the fossa. Elsewhere the cancellous bone is normal and contains red marrow. The tissue from the acetabulum is triangular, measuring 2 x 2.5 by 0.7 cm. One surface is smooth and red, the other irregular and mixed red and yellowish-white. The cut surface is mainly reddish-brown flecked with yellow and white areas and has the consistence of fibrous tissue.

Microscopic :- The synovial membrane (Fig. 20) is of areolar type with numerous villi. It is lined on its inner surface by one to six layers of plump polyhedral cells with little intercellular substance. The vessels in the core of the villi are often congested and cuffed with round cells, and similar cells occur in dense foci which include small vessels. The cells in the foci are mainly lymphocytes and plasma cells, the latter lying mainly towards the looser periphery of the foci. No collagen damage is seen. Though there is no recent haemorrhage, occasional deposits of haemosiderin are seen either in histiocytes or free in the tissues. The head of the femur shows thinning or complete absence of its articular cartilage. Where present the regular arrangement into layers is lost, the cells are swollen and lie in clumps of up to six cells. The matrix is normal. The surface of the cartilage, or where it is missing, the bone is covered by a layer of vascular collagenous connective tissue which shows a diffuse and focal infiltration with round cells. The bone trabeculae in the head are reduced in size and numbers and in the sections examined there is occasional osteoclastic absorption deep to the sub-chondral plate. The marrow spaces contain fat especially superficially, though the deeper ones contain some haemopoietic tissue. A few round cell para-vascular foci occur in the superficial spaces, but there is no granulation tissue here. The tissue from the acetabulum appears to/

to be synovial membrane of adipose type, but its architecture and cytology have been obscured by widespread haemorrhage, most of which is very recent. One edge is recognisable as a synovial surface and at one point shows villous formation with hyperplasia of surface cells, some of which are multinucleate. Most of the section consists of adipose connective tissue infiltrated with red cells and containing dense round cell foci similar to those already described. The vessels in and around the foci are mostly capillaries with swollen endothelium. Collagen fibres throughout the section are often swollen but not necrotic. Arterioles and arteries deep in the membrane have their walls considerably thickened by fibrosis of all coats and are occasionally thrombosed

Head and Neck of Left Femur and Soft Tissue from Hip Joint : Naked-eye :- Appearances are very similar to those in the other specimen, thus there are tags of villous synovial membrane at the junction of articular cartilage and bone, and prominent lipping of the anterior and posterior aspects of the articular surface. A good deal more normal articular cartilage is present than was seen on the head of the right femur. This is particularly so on the anterior surface, though here and there small tags of soft tissue are adherent. The fossa for the round ligament is larger than usual and around it, the cartilage is thin or has been replaced by semi-translucent soft tissue. On section, the cartilage is normal in thickness and appearance except near the fossa where it is thin. The cancellous bone is normal and contains red marrow. The soft tissue consists of three pieces of firm fibrous tissue with pale reddish-pink surfaces, measuring 2.8 by 1.0 by 0.5, 2.0 by 1.0 by 0.7 and 2.0 by 1.2 by 1.0 cm. respectively. On section the appearances are similar - firm white tissue with areas of congestion and haemorrhage.

Microscopic :- Blocks taken from the synovial membrane and the soft tissue all show the same type of tissue and the changes are the same as those already described for the previous specimen, viz., areolar type of synovial membrane with the following features -

i) villous architecture
ii) synovial cells several layers thick, with fibrinoid change affecting the surface in several places,
iii) very great congestion,
iv) focal and diffuse infiltration with round cells, and
v) a few areas of recent haemorrhage.

Around some of the capillaries, the fibrous tissue has a laminated distribution and some of the arterioles are thick-walled with occasional thrombosis.

Summary : The appearances in both these specimens are those of a chronic arthritis with destruction of the articular cartilage by granulation tissue and consequent fibrous ankylosis. The histological features in no way differ from those of rheumatoid arthritis.

and hips : also iritis. Tissue obtained from both hips.

Case 200.

M aged 34. Involvement of ankles, knees, hips, whole spine, elbows, wrists, fair and ankles. Tissue obtained from both hips.

Case 202.

M aged 26. Involvement of hips, knees, ankles, knees, lumbar and sacral spine, left shoulder, feet. Tissue obtained from left knee (Fig. 21).

Case 203.

M. Tissue obtained from a hip.

Material from Case 199 was obtained from both knees at autopsy. This was a very severe case in which all joints in the body were affected. The patient died of uraemia due to advanced amyloidosis.

Case 201.

M aged 49. Ref :- MHB 3717.
Involvement of sacro-iliac joints, whole spine and right sterno-clavicular joint. Tissue taken from the last-named. (Fig. 22).

SECTION II.

The following cases, already listed in Section I, were used in this Section - Cases 196, 197, 199, 201 and 203.

SECTION IV.

Case 199, listed above, was used in this Section.
Material from four more cases was obtained at biopsy :-

Case 205	Ref:- MHB 2851	right quadriceps	(1)
207		pectoralis	
208		quadriceps	(1)

and in a further three at autopsy.

Case 204.

M aged 67. Ref :- PM. 268/ 39.
Death from renal carcinoma with metastasis to lungs. Muscle was obtained from lumbar region of spine. This case was reported in detail by Freund (1942).

Case 206.

F aged 39. Ref :- PM 547/ 49.
Death from acute bronchopneumonia complicated bronchiectasis and chronic bronchitis. Muscle tissue obtained/

obtained from rectus abdominis, pectoralis major, diaphragm, psoas, quadriceps, deltoid.

Case 209.

M. Ref :- PM 345/51.
Death from bronchopneumonia and lung abscesses following ileostomy for long-standing ulcerative colitis. Muscle obtained from lumbar region of spine.

SECTION V.

The only case used in this section was Case 198.

OSTEO ARTHRITIS.

SECTION I.

In the following cases synovial tissue was obtained from the single joint named at surgical operation, usually arthroplasty :-

Case	210	Ref :- LII/655	shoulder in syringomyelia
	211	LIII/1054	hip
	212	LIII/112	right hip (Fig. 23)
	214	LII/1594	right hip (Fig. 24)
	215	XLI/290	right knee : other knee also affected.
	216	XLII/810	knee
	217	LII/1881	hip
	218	LII/2135	hip
	219	LIII/1078	hip (arthrokatadiasis).
	220	LIII/1595	knee (amputation for arteriosclerotic gangrene).
	221	LIII/1770	right hip
	222	LIII/1995	hip
	223	LIV/ 401	right hip (following slipped epiphysis).
	224	LIV/1271	hip
	225	LIV/1902	hip (following fractured neck of femur)
	226	LIV/2196	hip (post-traumatic)
	227	LIV/2383	right hip (post-traumatic)
	228	MHB 332	knee
	229	MHB 2720	hip
	230	MHB 3934	right sternoclavicular joint
	231	MHB 4026	right hip
	232	MHB 4671	knee
	233	MHB 632	right knee (Charcot joint)
	234	MHB 900	midtarsal joint(following flat foot and hallux rigidus) (Fig.25).
	235	MHA 2853	hip (bilateral arthrokatadiasis).
	236		right hip (amputation for arteriosclerotic gangrene).

In/

In Case 213 (MHA 4338) synovial tissue was obtained at autopsy from four lumbar intervertebral joints and the left lumbosacral joint, all of which showed well-marked osteoarthritis. The patient died of shock following emergency gastrectomy for haemorrhage from peptic ulcer.

SECTION IV.

The following cases which were used in this Section are listed above - Cases 220, 229 and 235.

The following living patients suffered from typical uncomplicated osteoarthritis, one small block being removed at biopsy by the writer from the muscle mentioned :-

Case 237	Ref:-	MHB 3538	right extensor wrist
238		LIII/1350	quadriceps
239		MHB 3847	right extensor wrist
240		MHB 3537	right extensor wrist

In the remaining two cases, a single block was obtained from the quadriceps at autopsy.

Case 241.

M. Ref :- PM 480/38.
Death from post operative shock following arthrodesis of Charcot knee : also tabes dorsalis and syphilitic acrtitis.

Case 242.

M aged 55. Ref :- MHA 2262.
Death from congestive cardiac failure following old myocardial infarcts : also subacute pyelonephritis, prostatitis and cystitis and severe acne. Previous cordotomy for osteoarthritis of hip.

SECTION V.

The only case used in this Section was Case 220.

GOUT.

Three cases provided all the material used in this thesis.

Case 243.

William K. aged 65.
Admitted 22.1.49 to Royal Infirmary, Ward 29.
Died 23.1.49.
Autopsy 24.1.49 by the writer (PM. 44/49)
Abstract of Case Notes :- The patient had been known "rheumatoid" since 1910 and had been pensioned off for many years. Became not so well 3 weeks ago, with abdominal discomfort and malaise. Too weak

to

to get out of bed in last two days. He developed acute breathlessness two days ago, unaccompanied by pain or any degree of cyanosis and in the last two days has continuously had to pant for breath. (Resp. 40/min. noisy and deep). Urinary output nil in last 24 hours before admission. P and T normal. B.P. 164/90. Prostate enlarged and the patient was catheterised. 7 ozs. of urine being taken off. This was clear of alb. and sugar and acetone : Given morphia ½ at 9 p.m. 22.1.49. Suddenly collapsed at 4.5 am. 23.1.49 and died at 4.10 a.m.

Macroscopic findings :-

The body was that of an elderly man of obese build, showing on external examination the changes of old established rheumatoid arthritis affecting the hands. The fingers of the right hand were in ulnar deviation and several of the small joints, particularly the proximal interphalangeal joints of the 2nd. 4th. and 5th. fingers were subluxated. There was, however, no obvious spindling of the fingers.

The wrist joint on the right side showed a moderate degree of limitation of movement. The left hand did not show any ulnar deviation but again several interphalangeal joints were subluxated, the affected fingers being considerably hyperextended. Subcutaneous nodules were present over the posterior border of both ulnae just below the elbow joint. The left knee showed a flexion deformity of about 45°, but there was no obvious swelling of this, or the other knee. The left knee was opened and found to contain about 5 cc. of pale, rather thick synovial fluid containing some small pieces of fibrinous debris. The synovial tissue did not show any recognisable hypertrophy nor was there any formation of granulation tissue over the articular surface of the bones. The articular cartilage of the femur and patella showed fairly extensive, but relatively early degenerative changes in that over much of the surface the smooth, translucent appearance was replaced by opaque, white material with a rough surface. Osteophytes were present at the margins of the articular surfaces. Rigor mortis was fully developed and lividity present on the posterior aspect. Autopsy was performed 31 hours after death.

Serous Sacs : Peritoneal sac : showed no abnormality.

Pleural cavities : In both pleural cavities old fibrous adhesions were present. These were most marked between the right upper lobe and the parietal pleura. There was no free fluid in either side.

Pericardial sac : Was completely obliterated by well formed, but fairly fine fibrous adhesions. There was no evidence of active inflammation.

Urogenital/

Urogenital System : Kidneys R 180 gms. L. 60 gms. The right kidney was normal in size and shape showing on external examination considerable irregularity of the cortical surface. On section the architecture of the kidney was largely disrupted, the cortex being considerably reduced and not easily differentiated from the medulla. All vessels showed considerable degree of thickening of their walls. The capsule stripped without much difficulty leaving a grossly granular surface.

Pelves and ureter showed no particular abnormality.

The left kidney was much smaller than normal and showed much the same features as the right except that the surface was much less granular. A single, large cortical cyst was present on this side. Pelvis and ureter were healthy.

Bladder : was healthy.

Prostate : Was enlarged to about twice its normal size showing on section the honey-combed appearance of senile hyperplasia.

Cardiovascular System : Heart : 900 gms. Was considerably larger than normal and showed a very great increase in subepicardial fat. Myocardium of the left ventricle was considerably hypertrophied and scattered throughout it were numerous flecks of fibrous tissue. There was no evidence of infarction. Elsewhere the myocardium appeared healthy. The endocardium showed no abnormality. Mitral valve admitted 5 fingers. Tricuspid 5 plus fingers. Coronary vessels showed fairly extensive but not severe atheromatous changes.

Aorta : showed a moderate degree of atheroma.

Respiratory System : Larynx, trachea and bronhi were slightly congest congested, but there was not much evidence of pathological change.

Lungs : R 980 gms. L 800 gms. Both lungs were normal in size and shape showing no abnormality on external examination. On section both were seen to be generally congested and oedematous but without any obvious evidence of bronchopneumonia.

Alimentary System : Mouth, tongue, pharynx, oesophagus, stomach and intestines : Were healthy.

Liver : 1700 gms. The liver was normal in size and shape showing no particular abnormality on external examination apart from the presence of a nodule measuring about 2 x 1 x 1 cm. at the extremity of the left lobe. This nodule was firmer in consistence than the rest of the liver, apparently encapsulated and of buff colour. Elsewhere the cut surface of the liver showed no abnormality.

Gall bladder, Biliary system : Were healthy.

Pancreas : Much of the tail and part of the body of the pancreas were occupied by a firm tumour which on section had the appearance of a carcinoma. Elsewhere the organ was firmer than normal, but there was no obvious tumour infiltration.

Lymphatic and Haemopoietic System : Spleen : 300 gms. Spleen was moderately enlarged and showed numerous/

numerous petechial haemorrhages in its capsule. On section the organ was congested but did not show any other evident abnormality.

Lymph Glands : No enlarged lymph glands were found anywhere in the body.

Mid Femoral marrow : Mid femoral marrow on the left side showed replacement of the fatty marrow by red, reactive tissue.

Endocrines : Pituitary, thyroid were healthy.

Suprarenals : A cortical adenoma about 1 cm. in diameter was present in the right suprarenal which elsewhere showed a moderate degree of nodular hyperplasia of the cortex. Left suprarenal appeared healthy.

Central Nervous System : No abnormality was found in the brain which was sectioned fresh.

Bacteriological Report : Synovial fluid : The specimen contained a few polymorphs, lymphocytes and " endothelial " cells. No organisms were found in the direct films or on culture.

Microscopic findings :-

Kidneys : Right : The whole architecture is greatly distorted, with many glomeruli represented by hyaline discs and many others partly fibrosed. The remaining glomeruli are larger than normal but this is not associated with inflammatory changes or with crescent formation. The tubules related to fibrosed glomeruli are atrophic and contain hyaline casts whereas the others are dilated and hypertrophic. One cortical retention cyst just over 1 mm. in diameter is lined by a single layer of columnar epithelium. Throughout the kidney there is marked diffuse and sometimes focal round cell infiltration and fibrosis. The medulla shows moderately severe congestion.

The afferent arterioles are sometimes thickened and hyaline and the small arteries show advanced and widespread hyperplastic sclerosis.

In addition to these findings there are scattered in the medulla small cystic structures some originating in collecting tubules containing coagulated albuminous fluid and small numbers of doubly refractile, golden brown, needle shaped crystals. The walls of these structures are lined with histiocytes and lymphocytes, giant cell forms of the former being common though none of them contains crystals. Here and there polymorphs are present, sometimes sufficiently numerous to form small abscesses, but always superimposed on the former change. The appearances are those seen in tophi, much as the nodules on the forearms in this case (see below).

Left : The ischaemic changes are much more advanced and small cysts are again seen. One large cyst in the medulla contains refractile crystals but its wall contains only small numbers of histiocytes and lymphocytes.

Two/

Two distinct lesions are thus present :-
a) diffuse hyperplastic sclerosis with benign nephro-sclerosis of advanced degree, and
b) urate deposits characteristic of gout.

Synovial Tissue and Subcutaneous Nodule : Blocks of synovial tissue were taken from the right sterno-clavicular joint and left knee joint (2). (Figs. 27, 28, 70 and 71). A section from the former shows the areolar type of membrane with many small villi. The synovial lining cells are hyperplastic sometimes to the extent of filling a villous but usually the surface layer is clearly distinguishable from the core of the villi. The villi also show infiltration with lymphocytes and histiocytes, often perivascular, proliferation of capillaries with swollen endothelium ; oedema ; fibrinoid necrosis of surface cells ; deposits of haemosiderin ; cysts similar to those in the kidney from which urates have been dissolved out. In the knee the membrane is also villous and shows the same features, though oedema is predominant. Urate deposition has occurred deep in the capsule.

The subcutaneous nodule co nsists of collagenous connective tissue containing numerous urate deposits. The walls of the cystic spaces are lined by a thin layer of histiocytes with numerous small foreign-body giant cells. The cysts are frequently in large groups separated by thin connective tissue septa and have frequently run together so that in one area there is a large cyst 3-4 mm. in diameter separated from the surrounding tissue by a well-defined collagen layer and showing in its centre the outlines of the smaller cysts which have coalesced to form it. Calcification has occurred in another fairly large cyst.

The nodule is thus a tophus and the changes in the joints are secondary to deposition of urates.

Lung : There is marked chronic venous congestion with some intra-alveolar haemorrhage, oedema and patches of early bronchopneumonia.

Liver : The liver cell nuclei towards the centre of the lobules are occasionally large and hyper-chromatic with prominent nuclei. Histiocytes in moderate numbers in the larger portal tracts, Kupffer cells and the liver cells themselves contain small yellow granules which give the Prussian Blue reaction, and there is slight excess of fibrous tissue in these tracts. Similar pigmented histiocytes are seen in the deeper part of the capsule. The nodule in the left lobe is clearly demarcated but not encapsulated. It consists of columns of liver cells often broader than normal with a disordered lobular pattern. The cells are mostly uniform but the nuclear irregularity noted elsewhere is again present. No mitotic figures are seen here or elsewhere. Occasional bile ducts are present in the nodule but no normal portal tracts. Haemosiderin in the nodule is confined to the Kupffer cells. There is no necrosis nor inflammation in/

in either section examined.

Pancreas : Much of the tissue is autolytic. No evidence of a carcinoma or other tumour is seen. Occasional groups of acini are dilated sometimes with marked thinning of the wall and the lumina contain a few polymorphs and histiocytes. One of these areas is associated with localised fibrosis of a lobule.

Spleen : There is marked congestion of sinusoids with deposits of haemosiderin in the pulp in considerable excess. The Malpighian corpuscles, trabeculae and capsule are normal. Arteries and arterioles show hyaline thickening but this is not excessive.

Suprarenals : The presence of a cortical adenoma and nodular hyperplasia of the cortex on the right side is confirmed.

Pituitary : N.A.D.

Mid-femoral Marrow : The marrow is moderately hyperplastic with mixed normoblastic and myelocytic picture. One small artery shows medial calcification.

Oesophagus : There is a slight degree of leukoplakia, i.e. mild focal hyperplasia of the epithelium with marked hydropic degeneration.

Skeletal Muscle : Sections from rectus abdominis, pectoral major, diaphragm, psoas, quadriceps and deltoid show no abnormality.

Peripheral Nerve : Sections from femoral nerve and branchial plexus show no abnormality.

Pathological findings :-

Gout with deposition of urates in kidneys, subcutaneous tissue, synovial tissue and joint capsule of left knee and right sterno-clavicular joint.
Benign nephrosclerosis of advanced degree. (Uraemia).
Hypertensive hypertrophy of left ventricular myocardium with fibrosis.
Pulmonary congestion, oedema and early bronchopneumonia.
Mild generalised and focal hyperplasia of liver cells and haemosiderin deposits in liver.
Mild pancreatosis.
Hyperplasia and adenoma of cortex of right suprarenal.

Case 244.

Synovial tissue from wrist, metacarpophalangeal joint and ankle in Pathological Museum, University of Edinburgh (Ref :- DB 549) (Fig. 26).

Case 245.

Tophus in Pathological Museum, University of Edinburgh (Ref :- DB 4897) (Figs. 122 and 123).

RHEUMATIC FEVER.

SECTION I.

Case 246.

M aged 49. Ref :- PM. 550/47.
Rheumatic fever of 10 days' duration causing severe carditis and involving shoulders, elbows, hands and knees. Previous attack 10 years previously. Synovial tissue obtained from left elbow, right hip and right knee.

Case 247.

M aged 13. Ref :- P.M. 562/49
Severe rheumatic carditis and aortitis. Synovial tissue obtained from knee.

Case 248.

M aged 54. Ref :- PM. 172/49
Death from cardiac failure during second attack of rheumatic fever. Synovial tissue obtained from knee (Fig. 29).

Case 249.

M aged 63.
Death from cardiac failure during initial attack of rheumatic fever. Most of the larger joints were involved and tissue was obtained from the right knee (Figs. 30-32).

Case 250.

M aged 20.
Death from acute cardiac failure during recurrence of rheumatic carditis. Only slight joint lesions :- tissue taken from right knee.

Case 251.

Douglas H. Aged 9
Admitted : October 1940 to Royal Infirmary, Ward 26.
Died 31.10.40.
Autopsy 1.11.40, by Prof. A.C.P. Campbell.
Abstract of Case Notes :- Two weeks ago patient had a sore throat and this was followed by polyarthritis and fever. Did not respond to Salicylate therapy or sulphapyridine. Developed endocarditis and pericarditis. Terminal congestion of the lungs with pleurisy occurred.

Macroscopic findings :-

The body was that of a boy of normal development for his age (9 years), reasonably nourished. The skin/

skin was pale. There was no oedema and no subcutaneous nodules could be felt. There was no obvious swelling of any of the joints. Post mortem rigidity and lividity were present.

Neck organs : Tongue : appeared normal.

Tonsils : Were slightly enlarged but showed no congestion and exuded no pus. Right tonsillar lymph node and the deep cervical lymph nodes at both sides were moderately enlarged, soft and congested.

Trachea and oesophagus : appeared healthy.

Thyroid gland : healthy.

Thorax :- Pericardial sac : Contained about 25 cc. of yellow, turbid, almost purulent fluid. There was no adhesions.

Heart : Was of normal size and shape ; it weighed 240 gms. Pericardium showed congestion and a little fibrinous exudate on the posterior surface of the auricles but elsewhere was mainly smooth and glistening. A small lymph node which was considerably congested and soft was found within the pericardial sac at the root of the pulmonary artery. Coronary arteries appeared healthy. There was no dilatation or hypertrophy of any of the chambers of the heart. The myocardium of the ventricles, especially the left ventricle, was pale and showed a vaguely patchy, yellowish accentuation of pallor in the inner third of the ventricular wall. No Aschoff bodies could be seen naked eye. The mitral valve showed on each cusp a row of small (pin-head), translucent, greyish yellow adherent vegetations along the line of closure. There was no thickening or deformity of the valve cusps or the chordae. As the heart was opened aseptically for bacteriological examination the diameters of the valve rings could not be measured. The other valves all appeared healthy. The myocardium lining the chambers showed no abnormality except that on the posterior wall of the left auricle it showed a slight granularity without congestion.

Pleural sacs : Each contained about 30 cc. of clear free fluid in which were occasional flakes of fibrin. There were no adhesions.

Lungs : Were voluminous and heavy. The right 520 gms. and left 400 gms. The left lung showed a trace of fibrinous exudate on its posterior surface. On section the greater part of both lungs, that is excepting only the most anterior portion, was of unduly firm and quite airless consistence, and was of a uniform brownish red colour indicating moderate congestion. The tissue had a rather translucent appearance. On squeezing it exuded copious fluid which was red and clear. It was not clear whether this undue firmness was due to oedema only or to oedema plus inflammatory consolidation. The clearness of the fluid suggests merely oedema, but the lung consistence was firmer than is usually seen with oedema alone. The iron reaction was negative. The bronchi showed no undue congestion and did not appear to contain inflammatory exudate.

Para-/

Para-tracheal lymph nodes : Were slightly enlarged, soft and uniformly congested.

Aorta : Appeared healthy.

Abdomen : Peritoneal Cavity : Contained a trace of clear free fluid. Peritoneum was healthy.

Liver : Was of normal size, 900 gms. The surface was smooth. On section it had an opaque appearance suggestive of cloudy swelling with a little central congestion of the lobules. Consistence was a little soft.

Gall bladder, bile ducts, pancreas and suprarenals : Appeared healthy.

Spleen : Size normal. 100 gms. Capsule was thin and wrinkled. On section the pulp was a uniform rather pale red colour. Malpighian bodies were small. Consistence was normal.

Stomach, small and large intestine : Appeared healthy.

Kidneys : Size normal, each weighing 90 gms. Capsule stripped easily leaving a smooth surface. Colour was a greyish pink, suggestive of cloudy swelling. Pelves appeared healthy.

Ureters, bladder and prostate : All appeared healthy.

Ileo-caecal lymph nodes : Were slightly enlarged, but showed no congestion.

Bone Marrow : The middle of the shaft of the femur showed the marrow cavity occupied by uniform dull red marrow.

L. Knee Joint : Was opened. It contained no effusion and the synovia showed no abnormality apart from a little congestion of that part clothing the cruciate ligaments.

Microscopic findings : Heart : The pericardium shows to a varying degree in different regions, an acute inflammatory reaction of fairly mild degree ; there is little or no surface exudate of fibrin. No Aschoff bodies are seen in the pericardium.

Myocardium : that of the left ventricle (particularly the inner part of the posterior wall) shows severe fatty degeneration of vaguely patchy distribution ; Aschoff bodies are seen in various parts of the myocardium ; they are especially numerous in the wall of the left ventricle adjacent to the attachment of the posterior mitral cusp ; they are mostly of the coronal type, showing central swelling and necrosis of the collagen fibres, and in some cases a little fibrin. As well as the Aschoff bodies there are areas of more diffuse polymorph infiltration of the connective tissue septa. The rings of the mitral, tricuspid and aortic valves show a considerable inflammatory reaction - swelling and proliferation of local connective tissue cells, infiltration with lymphocytes and polymorphs, and swelling of capillary endothelium : and a similar diffuse inflammatory reaction is well marked throughout the cusps of the mitral and aortic valves. Small hyaline or granular acellular vegetations are present on the proximal surface of the cusps of both/

both valves. The endocardium of the posterior wall of both auricles shows many large Aschoff bodies, as well as a more diffuse inflammatory infiltration ; and the left auricle shows plaques of new cellular connective tissue between endothelium and elastica.

The picture is that of an intense rheumatic pancarditis.

Aorta and pulmonary artery : Sections from the roots of these vessels show no lesions.

Tonsils : Each tonsil shows quite numerous large spindle-shaped Aschoff bodies in its capsule and in the immediately adjacent pharyngeal muscle. (Fig. 170). These Aschoff bodies are larger than those in the myocardium, and of the " polar " type, without any central necrosis. No definite inflammatory reaction can be seen in the substance of the tonsils.

Oesophagus : No lesions are seen in mucosa, muscle or surrounding connective tissue.

Lymph nodes : Tonsillar, deep cervical and tracheo-bronchial : all show a considerable acute inflammatory reaction (congestion, and histiocytic and polymorph infiltration of the sinuses) without any specific features.

Lungs : A section from each lower lobe shows a similar picture ; the striking feature is a bronchiolitis in which the respiratory bronchioles and alveolar ducts are lined by a hyaline membrane in most places giving a negative reaction for fibrin (phosphotungstic acid haematoxylin stain); there are also a good many polymorphs in these bronchioles. The alveoli show congestion, and a considerable catarrhal reaction, fairly diffuse but maximal around the bronchioles ; occasional alveoli contain fibrin and a few polymorphs ; there are only a few heart failure cells. The interlobar septa as well as the alveolar lumina show considerable oedema. The larger bronchioles appear normal. The picture is characteristic of, though not perhaps specific for, rheumatic pneumonia.

L. Knee Joint : Sections of the synovia show a little swelling, and proliferation of the covering cells and the immediately subjacent connective tissue cells. There is little or no congestion, no fibrinous or leucocytic exudation, no swelling of the collagen and no Aschoff bodies.

Liver : Shows slight C.V.C. and very slight fatty changes in the centres of the lobules.

Kidney, spleen and pancreas : show no abnormality.

Bacteriological Report : R. Pleural exudate : Cultures yielded growths of Streptococcus viridans and of Staphylococcus albus.

Pericardial exudate : Cultures yielded no growth.

Heart Blood : Cultures yielded no growth.

Lung tissue : Cultures yielded growths of Streptococcus viridans and af Streptococcus haemolyticus (which did not belong to Group A)

Tonsillar tissue : Cultures yielded growths of Staphylococcus/

Staphylococcus albus and Streptococcus viridans.
Tricuspid valve : Cultures yielded growths of an anthracoid (contaminant) only.
Mitral valve : Cultures yielded growths of a non-haemolytic (gamma) variety of Streptococcus.

Pathological diagnosis :-

Acute rheumatic pericarditis and myocarditis.
Acute rheumatic endocarditis, involving mitral and aortic valves.
Acute rheumatic peri-tonsillitis.
Rheumatic pneumonia.

Case 252.

F aged 25.
Death from cardiac failure in 27th. week of pregnancy due to acute rheumatic carditis superimposed on mitral stenosis. Synovial tissue obtained from right knee.

Case 253.

F aged 25.
Death from cardiac failure after premature labour : Recent acute rheumatic carditis. Synovial tissue obtained from right knee.

Case 254.

M aged 3
Death from cardiac failure approximately three weeks after onset of very severe rheumatic carditis: recent whooping cough. Synovial tissue obtained from right knee.

Cases 255 and 256.

Two cases of subacute bacterial endocarditis (Ref : P.M. 51/49 and MHA 2559). Synovial tissue taken from a knee in each.

SECTION II.

All the cases used for Section I, except Cases 255 and 256 were used in this Section also.

SECTION III.

Case 257.

Alexander McM. aged 13.
Attack of rheumatic fever three years previously affecting heart and joints, also subcutaneous nodules. Present attack began three weeks before admission and affected shoulders, elbows, hands, neck, ankles, left knee and foot. Double mitral and aortic murmurs present.
14.2.50 - Multiple subcutaneous nodules noted in extensor tendons left hand and flexor tendons right wrist.
3.3.50/

3.3.50 - Further nodules on occiput, both elbows and knees. Original nodules still present. Biopsy taken by the writer from right elbow (MHA 5803), the nodule being approximately two weeks old (Fig.124).
1.5.50 - Biopsy taken by the writer from nodule of approximately six weeks duration in occipital region (Figs. 125 and 126).

Case 258.

Nodule from case of rheumatic fever but by Dr. H.J. Gibson, Bath.

Case 259.

Nodule from case of rheumatic fever sent by Professor S.L. Baker, Manchester.

Case 260.

F aged 19. Ref :- MHB 8058.
Second attack of rheumatic fever, of three months' duration, associated with small nodules on occiput, right hand and left elbow and in flexor tendons of hands. Tissue taken from nodule over metacarpophalangeal joint.

Case 261.

F aged 38. Ref :- XLVII/ 46 and 190.
Third attack of rheumatic fever with nodules on elbows and over metacarpophalangeal joints. Biopsy from the latter site.

Case 262.

F aged 45. Ref :- MHB 2886.
See text, p. 165 and Fig. 133.

SECTION IV.

The following cases which were used in this Section are listed under Section I - Cases 246-251, 255 and 256.
In the following cases of uncomplicated active rheumatic carditis, one or more blocks of muscle (as indicated in brackets) were taken at autopsy -

Case	268	Ref :- PM.	424/47	(1)
	277		269/48	(5)
	280		346/48	(4)
	281		453/48	(5)

In three cases, active or healing rheumatic carditis was accompanied by some other lesion or lesions :-

Case	263	Ref :- PM.	244/37 (2)	acute glomerulonephritis
	273		172/48 (4)	acute appendicitis with perforation
	284	MHA	2982 (5)	cirrhosis of liver and

disseminated sclerosis.

Muscle was taken also from two cases of subacute bacterial endocarditis - Case 272, Ref :- PM.169/48, 3 blocks : Case 279, Ref :- PM. 343/48, 7 blocks -
and from 15 cases of healed rheumatic endocarditis (usually mitral stenosis) often accompanied by other conditions :-

Case 264	Ref:- PM.	592/46	(2)	bilateral popliteal embolism and renal infarct
265		31/47	(8)	aortic embolism : renal and splenic infarcts.
266		107/47	(2)	organising pneumonia
267		134/47	(1)	pulmonary infarcts
269		78/48	(3)	
270		87/48	(1)	carcinoma of pancreas
271		128/48	(2)	
274		183/48	(3)	anthracosilicosis, chr. bronchitis and emphysema
275		200/48	(3)	duodenal ulcer, haemorrhage and perforation
276		207/48	(3)	carcinoma of thyroid
278		270/48	(5)	glioblastoma multiforme
282	MHA	2726	(2)	
283		2799	(5)	cholelithiasis and hydrops gall bladder
285		3080		acute appendicitis and pelvic peritonitis
286	NP	2182		femoral embolism

SECTION V.

Cases 246 and 255 were again used in this Section, also the following cases of healed rheumatic endocarditis (usually mitral stenosis), often accompanied by other conditions :-

Case 287	Ref :- PM	136/50	(Fig.182)
288		137/50	acute bronchopneumonia
289		146/50	bronchopneumonia with haemorrhage into rect.
290		161/50	chronic pyelonephritis
291		180/50	myocardial infarction : benign nephrosclerosis
292		325/50	benign nephrosclerosis, cerebral haemorrhage
293		376/50	

SECTION VI. (Cases of calcified mitral stenosis in which sections were examined are marked with an asterisk).

1. Cases of active rheumatic carditis :-

The following have been listed previously :-

Cases/

Cases 246 to 252 and 254 - under Section I.
Cases 263, 268, 273, 277, 278 and 284 - under Section IV.
Other cases used, together with the indications of active carditis were :-

Case.	Ref :	
294	148/46	Aschoff bodies, left auricular (LA) endocarditis, arteritis.
295	308/40	Aschoff bodies, mitral (M), valvulitis
296	287/40	M valvulitis
298	347/47	Aschoff bodies, M. valvulitis
299	209/39	Pericarditis, myocarditis, tricuspid (T), M and aortic (A) valvulitis
300	223/39	Healing Aschoff bodies, M & A valvulitis
301	254/39	Aschoff bodies, M valvulitis arteritis
302	396/39	A valvulitis, left ventricular endocarditis
304	17/40	Aschoff bodies, A & M valvulitis
305	151/40	Aschoff bodies,A & M valvulitis, LA endocarditis, arteritis
306	365/40	Aschoff bodies, T and M valvulitis, LV endocarditis
307	471/40	Aschoff bodies, M valvulitis
308	455/41	Healing M valvulitis
309	443/43	Aschoff bodies, T, M & A valvulitis
312	28/46	M valvulitis
327	231/46	Healing Aschoff bodies, A valvulitis
332	305/46	M valvulitis
346	526/46	Aschoff bodies, M valvulitis
358	624/46	Aschoff bodies, A valvulitis
*371	157/47	Aschoff bodies
384	366/47	M & A valvulitis, LA endocarditis
397	131/48	LA endocarditis
408	381/48	Aschoff bodies, T, A & M valvulitis
455	557/49	Healing M & A valvulitis
460	640/49	Healing Aschoff bodies
484	MHA 3122	Aschoff bodies
*486	3178	Aschoff bodies, M valvulitis
497	3601	M valvulitis
*504	3822	Aschoff bodies
*509	EHA 803	M & A valvulitis
511	870	Aschoff bodies, M valvulitis
*512	875	Valvulitis
514	917	M valvulitis
516	929	M valvulitis
*522	LHA 380	Aschoff bodies, M & A valvulitis

2. Cases of active rheumatic carditis plus sub-acute bacterial endocarditis (SBE) :-

Case	Ref:	
297	PM 98/47	SBE aortic valve, M. valvulitis, myocarditis
343	460/46	SBE mitral and aortic valve, Aschoff bodies.

372/

372	PM 169/47	SBE mitral valve, Aschoff bodies
* 399	194/48	SBE mitral valve, Aschoff bodies
419	2/49	SBE mitral and aortic valves, Aschoff bodies
* 483	MHA 3086	SBE mitral and aortic valves, A valvulitis, Aschoff bodies.

3. Cases of inactive rheumatic carditis :-

The following have been listed previously :-
Case 253 - under Section I
Cases 264 to 267, 269 to 271, 274 to 276, 281 to 283 and 285 * - under Section IV and
Cases 287*, and 288 to 293 - under Section V.
Other cases, together with the evidence of rheumatic carditis are listed below :

Case	Ref :-	
310	PM 4/46	Mitral stenosis (MS)
* 311	9/46	MS with calcification
313	39/46	MS
314	67/46	MS, Aortic stenosis (AS).
315	72/46	MS
316	100/46	Mitral fibrosis (MF)
317	103/46	MF, aortic fibrosis (AF), non-specific myocarditis
318	127/46	MS with calcification, AS
319	130/46	MS
320	132/46	MS
321	135/46	MS with calcification
322	136/46	MS, AF (also syphilitic aortitis)
323	149/46	MF
324	159/46	MF
325	182/46	MS, AS both with calcification
326	206/46	MS with calcification
328	257/46	MF
330	267/46	MS, with calcification
333	307/46	MS
334	320/46	MS and AS both with calcification, tricuspid stenosis (TS).
335	348/46	MS
336	362/46	MF
337	386/46	MS, AF
338	388/46	MS
* 339	409/46	MS with calcification, AS.
340	442/46	MS
341	444/46	MS, AF
342	454/46	MS with calcification
344	485/46	MS
345	491/46	MS
347	542/46	MS
348	544/46	MS with calcification
349	547/46	MS
350	566/46	MS & AS both with calcification
351	571/46	MS with calcification, AF
352	579/46	MS, calcification of mitral ring

353/

Case	Ref :	
353	586/46	MS
*354	606/46	MS with calcification
355	607/46	MS, AF
356	610/46	MS, AS with calcification
359	648/46	MS, AS
360	649/46	MS
361	13/47	MF calcification of mitral ring
362	40/47	MS and AS both with calcification
363	50/47	MS, AF
364	60/47	MF (also myocardial infarction)
365	97/47	MS with calcification
366	103/47	MS, AF
*367	111/47	MS & AS both with calcification
368	129/47	MF
369	137/47	MS, AF
370	156/47	MF, AF
373	172/47	MS, AS
374	175/47	MS with calcification
375	185/47	MS
377	193/47	MS & AS both with calcification
378	197/47	MF with calcification
*379	268/47	MS & AS both with calcification
380	275/47	MF, calcification of mitral ring
381	280/47	MS, AS with calcification
382	322/47	MS, AS with calcification
383	341/47	MS, AS with calcification
386	505/47	MF
387	515/47	MF
388	517/47	MF, AF
389	519/47	MS & AS both with calcification
391	582/47	MS & AS both with calcification
393	4/48	MS, AS with calcification
394	38/48	MF with calcification
*395	56/48	Tricuspid fibrosis (TF) MS with calcification, AF
396	112/48	MF, AS with calcification
398	168/48	MF, AF
400	204/48	MS with calcification
*401	211/48	TF, MS with calcification, AS
402	243/48	TF, MS, AS
403	250/48	MF, AS with calcification
405	299/48	MS, AS
406	334/48	MS with calcification
407	356/48	MS, AS
409	406/48	MS
410	411/48	TF, MS
411	444/48	MS
412	467/48	MF, AS, left auricular endocardial fibrosis (LAF)
413	477/48	MS, AS
414	534/48	MS, AF
415	566/48	TF, LAF, MS with calcification, AF
416	572/48	MS, AF
417	594/48	MS, AF
418	599/48	MS
421/		

421	3/49	LAF, MF with calcification
423	6/49	MS, AS with calcification
424	10/49	MS, AF
425	12/49	TF, LAF, MS, AF
426	23/49	MS, AF
427	46/49	MS with calcification, AF
428	52/49	MS with calcification
429	55/49	MF with calcification
430	59/49	MF with calcification
431	66/49	LAF, MS, AS
432	75/49	MS, calcification of mitral ring
433	79/49	LAF, MS, AS
434	108/49	MS with calcification, AS
435	115/49	MS with calcification
436	121/49	LAF, MF
437	134/49	MF
438	140/49	MS
439	163/49	Tricuspid stenosis (TS), MF
440	182/49	MF
441	198/49	MS & AS both with calcification
442	234/49	LAF, MF
443	236/49	MF, AF
444	263/49	MS
445	292/49	TF, MS, AF
446	348/49	MS
447	364/49	MF
449	372/49	MF
450	384/49	MS with calcification
451	402/49	MS, AS (also myocardial infarct)
452	439/49	MS, AS
* 453	542/49	Pulmonary stenosis (PS), MS, AF
454	554/49	MS
456	581/49	MS with calcification, AF
458	603/49	MS
459	622/49	TF, LAF, MS, AF
* 461	135/50	MS with calcification, AF
462	558/50	MF
463	572/50	MS, AF
464	732/50	MS
* 465	735/50	MS with calcification (Fig.237).
466	2/51	MS with calcification, AF
467	3/51	MS & AS both with calcification
468	90/51	TS, MS with calcification, AS
469	136/51	MS with calcification
470	167/51	MS with calcification, AS
471	173/51	TS, MS
472	287/51	MS
473	333/51	TF, MS, AF
474	386/51	LAF, MS, AS
475	488/51	TF, MS, AS with calcification
476	MHA 2448	MS with calcification, AF
477	2451	MS, AS with calcification
478	2588	MS with calcification
479	2826	MS
480	2956	MS, AF with calcification
481	2999	MS with calcification
482	3043	MS
* 485	3136	LAF, MS & AS both with calcification (Fig. 238)
* 487	3200	MS with calcification
488/		

488	MHA	3213	LAF, MS, AF
* 489		3271	TS & MF both with calcification, PS, AF
* 490		3298	TF, MS with calcification, AS
492		3363	MS
493		3375	MF, AS with calcification
* 494		3381	MS
495		3487	TF, LAF, MS, AF
496		3545	MF
* 498		3616	MS with calcification, AF
499		3641	MS, AF
500		3642	TF, MS & AS both with calcification
501		3681	MS,AS with calcification
502		3685	MF
503		3779	MS
505		3916	TS, MS, AF
506		3937	MS, & AS both with calcification
507		3991	TS, LAF, MS
508		4002	MS, AS
* 510	EHA	838	LAF, MS
513		908	MF
* 516		1010	MF with calcification
517		1047	MS, AF
* 519		1209	LAF, MS with calcification
519		1216	MS
* 520		1273	MF with calcification
* 521		1404	MS with calcification, AF

4. Cases of inactive rheumatic carditis plus bacterial endocarditis :-

Case	Ref :		
255	PM	51/49	SBE mitral valve and left auricle, MF, AF
272		169/48	SBE mitral valve, LAF, MF
279		343/48	SBE aortic valve, MF, AF, calcification of aortic ring
303		8/40	SBE mitral valve, MF, AF
329		261/46	SBE mitral valve, MF
331		295/46	SBE mitral valve and aortic valve, MS
357		616/46	SBE aortic valve, MF, AF
376		186/47	SBE mitral valve, MF
385		426/47	SBE mitral valve, TF, MS, AF
390		528/47	SBE mitral and aortic valve, MS, AF
392		599/47	SBE mitral valve, MF
404		262/48	SBE mitral valve, MF, AF
417		575/48	SBE mitral valve and left auricle, MF, AF
421		4/49	SBE mitral valve, LAF, MF
448		366/49	SBE mitral valve, TF, MF
457		593/49	SBE mitral valve, MF
491	MHA	3357	acute BE mitral valve, MS

SYSTEMIC LUPUS ERYTHEMATOSUS.

Case 523.

Mrs./

Mrs. Mary H. aged 45.
Admitted 6.5.49 to Royal Infirmary, Ward 25.
Died 18.6.49
Autopsy 18.6.49 by Professor A.C.P. Campbell (PM 310/49).

Abstract of Case Notes :- Sudden onset of pleuritic pain 7 weeks before admission : subsided after sulphonamide treatment, but breathlessness still present. Pain returned with fevere and severe rash. No improvement on further chemotherapy. Five months previously there had been transient swelling and pain in hands and knees. No history of rheumatic fever. On admission - left pleural effusion, morbilliform rash on anterior aspect trunk and extensor surface limbs, albuminuria, BSR 104 mm/hr, Wbc 8600 (normal differential count). Blood culture repeatedly negative. BUN 120 mgm.%. No response to Salicylates, sulphonamides or penicillin. Chest signs persisted and were accompanied by extreme muscle tenderness and occasional joint pains. Died in coma.

Macroscopic findings :-

Autopsy 9 hrs. after death. The body was that of a woman looking about 45, of average build, well nourished but not obese. The skin was of normal cadaveric colour generally. No jaundice. Sparse groups of small dull purple spots resembling a fading purpura were seen on trunk, arms, legs and backs of fingers. The anterior aspect of the neck showed slight diffuse brown pigmentation with slight scaliness which appeared to be something rather more than mere exposure change. There was no sign of any butterfly rash on the face. There was no oedema.

Head : Skull, dura and venous sinuses : N.A.D.

Brain : Showed no external abnormality. It was sent uncut to the Neuro-Path. department.

Mouth : Edentulous. Sparse ulcers up to 8 mm. in diameter were seen on upper and lower gums exposing the bone. They showed no congestion. The tongue showed two small, slightly congested, fissured ulcers without any generalised change.

Axillary lymph nodes : Showed considerable enlargement, the nodes being very soft and deeply congested on section.

Neck & Thorax : Deep cervical lymph nodes on both sides showed moderate enlargement and were of similar appearance to those in the axilla.

Larynx : Showed extensive ulceration exposing the cartilage along the upper border of the epiglottis. Small foci of yellow necrosis and ulceration were seen on both vocal cords.

Trachea, Oesophagus, and Thyroid gland : N.A.D.

Pericardial Sac : Contained about 50 cc. of slightly turbid yellow fluid which was taken for culture. The parietal and visceral pericardium were considerably congested and showed fairly copious fibrinous exudate.

Heart/

Heart : showed slight globular enlargement : it weighed 410 gms. The epicardium showed generalised pericarditis as described. Coronary arteries appeared healthy. No nodular lesions were seen on them. The heart showed slight general dilatation. No definite hypertrophy was seen. Tricuspid valve admitted 3 fingers, mitral 2½ fingers (slightly dilated). The endocardium showed an atypical verrucose endocarditis. Small isolated brown, firmly adherent vegetations up to 3 mm. in diameter were seen (1) on the aortic aspect of the anterior aortic cusp (2) on the line of closure of the right posterior aortic cusp and (3) on the posterior wall of the left auricle high up near the septum. Valve cusps showed no sign of old fibrous thickening. Myocardium was of uniform, slightly pale brownish colour. It showed no focal lesions.

Pleural sacs : Both showed widespread fibrinous adhesions, which in places were sufficiently resistent to separation to suggest early organisation. There were small pockets of turbid yellow fluid.

Lungs : were of normal volume but slightly heavy, right 620 gms. L 480 gms. In each the pleura showed a widespread fibrinous pleurisy. On section the lungs were moderately congested and slightly oedematous, the oedema being more marked in the right. No focal lesions were seen.

Aorta : N.A.D. There was very little atheroma, considerably less than average for her age.

Ductus arteriosus closed. Pulmonary artery : N.A.D.

Abdomen : Contained a trace of clear free fluid. There were localised fibrinous adhesions between diaphragm and spleen. The peritoneum elsewhere appeared healthy.

Stomach and bowel : N.A.D. No dilatation.

Mesenteric vessels : numerous grey or reddish grey, strictly localised, nodular, concentric swellings were seen on the small arteries near and at the attachment of mesentery to bowel. These were most marked in the jejunal mesentery. The larger mesenteric arteries appeared healthy. Mesenteric and para-aortic lymph nodes N.A.D. No enlargement.

Liver : Size normal. Weight 1460 gms. Surface smooth. On section it showed moderate nutmeg mottling, the lobular peripheries being of unduly pale brown colour. Consistence slightly soft.

Gall bladder : Appeared healthy. It contained dark olive green bile.

Bile Ducts & Pancreas : N.A.D. The main pancreatic duct opened into the ampulla 8 mm. from its mouth.

Suprarenals : N.A.D.

Spleen : Was slightly enlarged weighing 210 gms. Capsule showed patchy fibrinous exudate. On section the Malpighian bodies were unduly large and prominent, with more clear cut margins than usual. Some were of rather yellow colour. The trabeculae also/

also appeared more prominent than usual as unduly pale white streaks. The pulp was moderately congested and slightly soft.

Kidneys : Were slightly enlarged, R 210 gms. L 230 gms. In each the capsule stripped easily leaving a smooth surface apart from a small, slightly depressed area in the right kidney suggesting a contracting infarct. The surface was slightly congested. On section cortex and medulla showed moderate uniform congestion. No focal lesions could be seen. Pelves healthy.

Ureters, bladder and uterus : N.A.D.

Ovaries : Left ovary showed a chocolate cyst 12 mm. in diameter, otherwise N.A.D.

Bone marrow : Middle of the shaft of femur was occupied by uniform dull red marrow.

Skeletal Muscle : The various skeletal muscles examined in trunk and upper and lower limbs showed no obvious abnormality.

Joints : Left knee and left ankle were examined. The cavities contained small effusions of clear mucoid fluid. The synovia showed slight patchy congestion near its attachment to the bone.

The articular cartilage appeared normal.

Bacteriological Report : Cardiac fluid : Films contained some polymorphonuclears and endothelial cells, but no organisms and culture was sterile.

Blood culture : A haemolytic streptococcal growth was obtained on culture.

Microscopic findings :

Heart : Pericardium : shows a marked fibrinous pericarditis in a stage of early organisation ; the inflammatory cells are mainly plasma cells - polymorphs are very scanty. There are no specific features.

Myocardium : shows a mild myocarditis - small foci of plasma cell and histiocytic infiltration of interstitium, in walls of both ventricles and auricles. L. ventricle also shows a few old para-vascular scars, very suggestive of former rheumatism.

Endocardium : aortic cusp - section confirms a vegetation of the aortic side of the cusp : the underlying valve tissue shows a focus of fibrinoid degeneration with plasma cell, lymphocyte and fibroblastic proliferation : similar but smaller foci without vegetations are present elsewhere through the cusp. The vegetation consists of platelet-fibrin thrombus. Mitral cusps (posterior); the angle between cusp and ventricular wall shows an area of endocarditis - gross fibrinoid infiltration of the collagen with a cellular reaction as above ; there is no vegetation over this focus.

Aorta (root) : N.A.D.

Mesenteric artery : Section through one of the nodular thickenings shows a very severe acute arteritis - complete disintegration of the wall with

copious/

copious polymorph infiltration (almost purulent) : the lumen is thrombosed.

Spleen : shows dense, relatively acellular, collagenous fibrosis around the central arterioles of the Malpighian bodies (characteristic lesion of L.E.D. as described by Klemperer et al). Sometimes a finer fibrosis extends out into the surrounding pulp. The arterioles themselves appear remarkably normal. The capsule and trabeculae show occasional small foci of plasma cell and lymphocytic infiltration with loosening and slight fibrinoid change of the collagen. The pulp shows considerable plasma cell infiltration. There is one small area of acute necrosis (presumably infarction).

Liver : shows marked acute centrilobular necrosis, affecting almost every lobule : the peripheries of the lobules show marked fatty degeneration.

Kidney : most of the glomeruli show the characteristic change -hyaline, sometimes fibrinoid thickening of capillary basement membranes, sometimes irregular, sometimes concentric (wire-loop appearance). There is little or no cellular proliferation in the tufts, but many show a peri-capsular fibrosis. A few tufts are grossly shrunken and avascular. The tubules show colloid droplet change, and many contain R.B.C.s : occasional small areas show atrophy of tubules. There are frequent small foci of inflammatory infiltration (plasma cells) in the interstitium of the medulla - not apparently related to tubular damage. The arteries and arterioles show no lesions.

Adrenal : shows acute/subacute arteritis of several capsular arterioles - cellular intimal fibrosis, fine granular bile-staining deposits in the media, and patchy fibrinoid degeneration in adventitia, with fibroblastic and histiocytic infiltration. The cortex shows a considerable area of focal necrosis.

Lung : gross congestion, purulent bronchiolitis and early bronchopneumonia ; no specific lesions.

Oesophagus : (lower third) shows a mild subacute oesophagitis of banal type. The adventitia is oedematous, with mild histiocytic and fibroblastic proliferation ; one or two arterioles in it show slight focal granular (blue-staining) degeneration of media.

Pancreas : N.A.D.

Bone Marrow (mid femur) : shows mild hyperplasia of banal myelocytic-normoblastic type. No unusual cells (the so-called " L.E. cells") could be seen.

Axillary lymph node : no follicles remain. The pulp shows diffuse oedema, granular thickening of the reticulin, and a profuse plasma cell infiltration. No fibrinoid change.

Sciatic nerve : one bundle shows a small focus of plasma cell infiltration.

Skeletal muscle : rectus abdominus - a single small focus of necrosis and fragmentation of muscle fibres, with fibrinoid degeneration of the interstitium.

Quadriceps/

Quadriceps and gastrocnemius : non-specific wasting only. Diaphragm and flexor carpi ulnaris N.A.D.

L. Knee joint : Acute necrotising vasculitis of arterioles and ? venules in synovia and surrounding tissue ; haemorrhage and patchy fibrinoid degeneration of synovia ; moderate hyperplasia of synovial lining cells ; a little surface fibrinoid exudate.

Skin : Neck - very definite inflammatory changes, compatible with L.E. - patchy oedema and plasma cell, lymphocyte and histiocyte infiltration of papillary layer ; considerable diffuse hyperkeratosis with horny plugging ; atrophy of Malpighian layer of epidermis.

Dorsum of finger : Similar but very much slighter changes.

Upper arm : Hyperkeratosis and horny plugging, but little or no inflammatory reaction.

Addendum to report (P. Cruickshank)

Skeletal muscles : Blocks were taken from rectus abdominis (2), pectoralis major, diaphragm (2), psoas, quadriceps (2), gastrocnemius, deltoid and flexor carpi ulnaris. Very occasional lymphorrhages were seen and more frequent foci in which degeneration or necrosis of perimysial collagen was accompanied by lymphocytic and histiocytic infiltration. Patchy atrophy or degeneration of muscle fibres also present.

Peripheral Nerves : Blocks were taken from sciatic nerve (2), brachial plexus (2) and femoral nerve (3). Lesions were similar to those in muscle with the additional feature of organising arteritis in some sections.

Pathological Diagnosis :-

Systemic lupus erythematosus :-
- typical lesion of skin
- verrucose endocarditis
- acute fibrinous pericarditis
- focal myocarditis
- acute fibrinous pleurisy
- polyarteritis of mesenteric and other vessels
- glomerular degeneration in kidneys
- periarteriolar fibrosis and focal capsulitis of spleen
- acute synovitis knees and ankle
- centrilobular necrosis of liver
- focal necrosis of adrenal
- cervical and axillary lymphadenitis

Ulceration of gums, tongue and larynx
Bronchitis and bronchopneumonia
Haemolytic streptococcal septicaemia.

Case 524.

F aged 38. Ref :- PM 459/49.

Illness commenced in joints, but also involved pleura, skin and kidneys clinically. Death in coma. Pathological examination revealed involvement of heart, kidneys, spleen, muscles, nerves and knees./

knees. Synovial tissue obtained from both knees (Fig. 33), muscle from rectus abdominis, pectoralis major, diaphragm, psoas and quadriceps and nerve from brachial and femoral plexuses.

Case 525.

F aged 15. Ref :- MHA 3709
Illness commenced in joints and also involved skin and kidneys clinically. Also meningococcal meningitis. Pathological examination revealed involvement of kidneys, spleen, skeletal muscle, palmar tendon sheaths and oesophagus. Synovial tissue obtained from tendon sheaths (Fig. 57) and right knee, muscle from rectus abdominis, pectoralis major, diaphragm, psoas, quadriceps, deltoid and tongue and nerve from brachial and femoral plexuses.

Case 526.

F aged 37. Ref :- MHA 4015
Illness commenced in joints and also involved skin, kidneys and lymph nodes clinically. Also pneumococcal septicaemia. Pathological involvement revealed involvement of heart, lungs, pancreas, kidneys, spleen, lymph nodes, pituitary, thyroid, suprarenals, skeletal muscle, right knee, palmar tendon sheaths (Figs. 58 and 59) and joints of third right finger (Fig. 35), muscle from rectus abdominis, pectoralis major, diaphragm, psoas and quadriceps (Fig. 171).

Case 527.

F aged 61. Ref :- PM. 171/40.
Involvement of kidneys, skin and muscle. Only the latter studied for this thesis.

DERMATOMYOSITIS.

Case 528.

F aged 70. Ref :- PM. 16/47.
Generalised urticaria and skin oedema, dysphagia, stiffness and pain around large joints. Also carcinoma of sigmoid colon with metastasis to liver.

Case 529.

Ernest P. aged 12.
Admitted to Royal Infirmary, Ward 48.
Died 23.1.46
Autopsy 24.1.46 by Prof. A.C.P. Campbell (PM. 42/46).
Abstract of Case Notes :- 5 years duration - generalised eruption - oedema of face, numerous

ulcerations/

ulcerations (all swabs showed haem. streps., staphs and B. proteus, no K.L.B.) of face, arms and legs. Skin changes are telangiectasia, reticulate pigmentation and atrophy. Muscular pain in limbs with marked atrophy. Patient suddenly went pulseless - ? cause of death.

Macroscopic findings :-

The body was that of a boy, poorly developed, looking nearer 10 than 12. He showed widespread lesions of the skin affecting mainly face, neck (back and front), arms and forearms, buttocks, thighs, legs and feet, and only sparsely affecting the trunk. The lesions were of various sorts and stages. The most acute consisted of areas of superficial ulceration in most cases not penetrating through the cutis vera, up to about 4 cm. in diameter, with reddish brown congested base and slightly rolled margin, cyanotic for several mm. around. Only one of these active lesions extended more deeply, i.e. one on the antero-lateral aspect of the right leg which showed necrosis of cutis vera in the form of a yellow slough, with small purulent sinuses. There was a series of less acute or healing lesions varying from the above described to lesions with recent re-epithelisation and still congested margin, and to lesions with central area of pale atrophic skin surrounded by a brown pigmented zone. In these healed lesions the degree of scarring varied from minimal to sometimes considerable thickening and puckering presumably indicating the site of an ulcer deeper than most. Large active lesions were seen on right foot and leg, face (chin, upper lip and nostrils), and back of neck. In addition to these obvious active or healed areas of ulceration there were also numerous areas of telangiectasis predominantly on forearms and thighs. These varied from small groups of pin head blue discoloured spots to almost confluent large areas. There were also areas of patchy reticulate brown pigmentation whihh did not appear to be related to previous ulceration. There was a considerable diffuse oedema of the face and of the lower legs and feet. The peroneal muscles and calves showed very considerable generalised wasting, and the vasti muscles of the thighs showed a slighter degree of wasting. On section, however, these muscles showed no obvious abnormality apart from general pallor which was quite definite, affecting all the voluntary muscle of the body (? due to anaemia). The interosseous and other small muscles of the hands showed no wasting. Post mortem rigor and lividity were present.

Head : Dura and venous sinuses appeared healthy. The brain appeared slightly shrunken, the sulci gaping unduly. The pia-arachnoid and basal vessels were healthy and no lesions were found on section. The pituitary body was of normal size.

Mouth & Neck : Tongue, Tonsils, pharynx, trachea and oesophagus - All showed no abnormality.

Thyroid/

Thyroid gland - Was rather small. On section both lobes were of uniform dark red, slightly gelatinous appearance.

Deep cervical Lymph nodes - Showed mild enlargement and were soft and grey pink on section.

Thorax : Pericardial Sac - Contained about 80 cc. of clear yellow free fluid with occasional flakes of fibrin ; no adhesions.

Heart : Size and shape normal ; weight 160 gms. The pericardium showed a localised area of delicate early fibrinous exudate on the anterior surface of the right ventricle. Coronary arteries were healthy. The myocardium showed a generalised uniform, slight pallor and was of flabby consistence. There was no hypertrophy or dilatation of any chamber. All valve cusps appeared healthy. The foramen ovale was closed.

Aorta : showed no abnormality. The ductus arteriosus was normally closed.

Pleural sacs - Each contained about 200 cc. of clear yellow free fluid, and each showed delicate adhesions at posterior surface of lower lobe.

Lungs : R 380 gms. L 270 gms. The lungs were of normal weight and volume. the left weighing 270 gms. and right 380 gms. The pleura was healthy apart from fibrous adhesions as above. On section both lungs showed a mild degree of general oedema but no appreciable general congestion. The middle lobe of the right lung showed an area of a few cubic centimeters size, of uniform, greyish-red consolidation, in the middle of which two or three small abscess cavities oozing yellow pus were seen, giving the impression of metastatic abscesses with surrounding consolidation. No other evidence of bronchitis or pneumonia was seen.

Tracheo-bronchial Lymph Nodes - Showed a moderate degree of enlargement being fleshy, soft and deep greyish red on section.

Abdomen : Peritoneal cavity - Contained about 100-200 cc. of clear free fluid. The peritoneum was healthy apart from occasional 3 or 4 mm. haemorrhages in omentum, transverse meso-colon and mesentery.

Stomach and Bowel - Showed no abnormality. The faecal contents throughout the bowel were of pale clay colour.

Liver - Appeared slightly enlarged weighing 1200 gms. The surface was smooth. On section the liver was of a peculiar orange yellow colour with increased lobular mottling, the centres of the lobules appearing darker, with, in addition, an irregular fine, rather ill-defined haemorrhagic mottling not definitely related to lobular patterh. The consistence was slightly softened.

Gall bladder - was flaccid. It contained thin orange coloured bile.

Bile ducts - Appeared healthy. There was no evident obstruction.

Pancreas : Nothing abnormal.

Suprarenals : Nil abnormal.

Spleen/

moderate congestion and a good deal of haemorrhage. The vessels show both acute and chronic arteritis.

An area of reticulate pigmentation shows small groups of brown pigmented histiocytes in the superficial cutis vera. The pigment gives a negative iron reaction. Inflammatory changes are relatively mild in this area. The explanation of the pigmentation is not clear.

Skeletal Muscle : Blocks examined from interossei of hands, and from biceps shows a similar picture - a marked (in places intense) semi-focal inflammatory infiltration (lymphocytes +++ , plasma cells), slight congestion, no obvious necrosis of muscle fibres, but considerable atrophy of some, and small groups of newly regenerated fibres ; arteries and arterioles frequently show arteritis as in the skin. Diaphragm shows only a slight focal infiltration.

Tongue : The skeletal muscle of the tongue is particularly severely affected by the above inflammatory changes, but vascular lesions are slight. The mucosa shows a brisk lymphocyte - plasma cell infiltration also.

Pharynx & Oesophagus : Sections show a mild focal lymphocytic infiltration of mucosa ; and a mild but quite definite focal infiltration of muscle coats (including both the voluntary muscle of the pharynx and the plain muscle of the oesophagus) with fairly frequent arteritis as above described.

Myocardium : (L. ventricle). shows a focal myocarditis - focal infiltrations of lymphocytes, plasma cells, histiocytes and a few eosinophils (not noticed in the lesions elsewhere): in addition to these acute or subacute lesions there are small patches of fibrosis indicating sites of healing of older similar foci. But no arteritis is seen.

Lung : A section from the consolidated area shows as the most striking feature an acute arteritis and arteriolitis ; very many vessels, both bronchial and pulmonary, show an acute fibrinoid necrosis of intima or of the entire wall, with a little cellular infiltration, including a few polymorphs. Few or no vessels show the more chronic lesions seen in other organs. The perivascular adventitia shows a dense small mononuclear infiltration, which extends throughout most of the interstitial tissues ; these are also oedematous and show an early fibrosis, indicating a subacute interstitial pneumonia. The consolidation is mainly due to this, but here and there there are small patches of alveolar exudate (fibrin a few polymorphs). Mainly however the alveoli contain only catarrhal cells. Many bronchi show a purulent bronchitis. The overlying pleura shows a mild fibrinous pleurisy. A section of lung remote from this patch of consolidation shows merely congestion and a rather marked perivascular and peribronchial lymphocytic infiltration, but no arteritis.

Tracheo-bronchial lymph node : Shows merely acute inflammatory reaction of the ordinary type.

No/

No arteritis.

Spleen : Pulp shows congestion and mild acute infective reaction (polymorph and plasma cell infiltration). Vessels healthy apart from mild hyalinosis of occasional arterioles.

Liver : Marked chronic venous congestion and marked fatty degeneration (peripheral). No arterial changes.

Kidney : Remarkably normal. No arterial changes.

Suprarenal : N.A.D. (A small artery in surrounding fat shows acute arteritis.

Pancreas, Thyroid, Pituitary : N.A.D.

Pathological diagnosis :-

Poikilo-dermato-myositis : Focal dermatitis - acute and chronic. Wide-spread myositis (of skeletal and plain muscle)
Arteritis and arteriolitis, acute and chronic, of many organs, including :
Acute pulmonary arteritis with interstitial pneumonia and fibrinous pleurisy.
Focal myocarditis.
Fibrinous pericarditis.
Chronic venous congestion and fatty degeneration of liver.
Infective splenic reaction.
Haemolytic streptococcal septicaemia
Infarction of testis.

Cases 530 to 534.

Biopsies were taken from individual muscles in each of these cases.

SCLERODERMA.

Case 537.

Mrs. Mary W. Aged 48.
Admitted to Royal Infirmary, Ward 28.
Died 30.12.46
Autopsy 30.12.46 by Professor A.C.P. Campbell (PM. 644/46).

Abstract of Case Notes :- Many months in ward with scleroderma. Gradually became more emaciated with evidence of congestive cardiac failure.

Macroscopic finding :-

The body was that of a middle aged woman of slight build, lean but not emaciated. There was no oedema and no jaundice or other generalised pigmentation. The skin in various parts of the body showed a diffuse leathery thickening, most marked over the calves, but uniformly present over the abdomen and to a less extent on flexor aspect of forearms and face. In addition to the induration

described/

described the skin of the abdomen showed a branny scaliness with numerous small circular, slightly raised, slightly brownish accentuatedly scaly patches. The anterior aspect of the ankles and the dorsum of the foot on both sides showed sites of old healed ulceration with brown pigmented margins and a pale, thin, rather glazed central skin. Various skeletal muscles were examined (calf, thigh, flexor, carpi ulnaris, pectoralis major, etc.), but apart from generalised palor no abnormality could be seen. The muscles in general appeared to be rather wasted but not exceptionally so for a woman of her age and build. Hands were unusually small. The terminal I.P. joint of all fingers showed a contracture and pulps of the fingers and to a greater extent of the thumbs showed considerable thickening, giving a rather clubbed appearance : but nails showed no clubbing.

Head : Skull, dura and venous sinuses : N.A.D.

Brain : Was of normal size showing neither swelling nor atrophy. Pia-arachnoid and basal arteries appeared healthy. No lesions were seen on section. Pituitary body appeared macroscopically normal.

Mouth & Neck : Tongue, pharynx, trachea, oesophagus and thyroid gland : All appeared normal.

Cervical lymph nodes : Several slightly enlarged lymph nodes were found in the left posterior triangle which on section showed areas of old caseation and calcification without any appearance of activity.

Thorax : Pleural Sacs : Contained a considerable amount of clear yellow, free fluid about 700 cc. in the right and 200 cc. in the left. The right sac showed a band-like old fibrous adhesion to the lateral aspect of the lower lobe and the left sac showed old diaphragmatic fibrous adhesions.

Lungs : Were of normal weight and volume each weighing 490 gms. The pleura was smooth and shining. The pleural surfaces showed a remarkable finely lobulated appearance from the presence of innumerable small cysts, for the most part apparently air containing. Superficially these resembled emphysematous bullae but unlike emphysema they were not especially concentrated at the borders of the lung but were uniformly distributed. The right lung was kept uncut. The left lung on section showed a lower lobe riddled throughout by cysts of all sizes up to 2 cm. in diameter, smooth walled, some apparently empty, some containing frothy mucus and some filled with peculiar pultaceous grey-brown material rather suggestive if inspired food. (This material was seen in 2 cysts). Between the cysts the lung tissue showed streaky fibrosis. The lower lobe showed no normal lung tissue at all. The upper lobe showed relatively normal lung tissue through most of its substance, cystic change being confined to the subpleural zone. These cysts appeared to be communicating with the bronchial tree but were not associated with any dilatation of larger or medium

sized/

sized bronchi. There was no evidence of any superadded pneumonia.

Pericardial sac : Contained about 150 cc. of clear yellow free fluid. No adhesions.

Heart : Was slightly enlarged weighing 330 gms. Its shape was preserved. Pericardium and coronary arteries were healthy. There was little or no dilatation of any of the chambers, but both right and left ventricles showed a mild but definite degree of hypertrophy. Myocardium was normal in colour and consistence. The tricuspid valve admitted 3 fingers and the mitral 2 fingers. The valve cusps and the endocardium elsewhere showed no abnormalities.

Aorta : Showed a relatively mild degree of atheroma. Ductus arteriosus was closed.

Abdomen : Peritoneal sac : Contained 300 or 400 cc. of clear free fluid. The peritoneum was healthy.

Stomach and Bowel : Showed no abnormalities. No atrophy detected.

Liver : Was of normal size (1520 gms.) Surface was smooth. On section it showed a slight degree of nutmeg mottling indicating chronic venous congestion. Consistence was normal. No focal lesion was seen.

Gall bladder : N.A.D. It contained dark green bile.

Bile ducts, Pancreas & Suprarenals : N.A.D.

Spleen : Was considerably enlarged weighing 305 gms. The capsule was smooth and healthy. On section the pulp generally was of normal deep red colour but slightly softened consistence. Malpighian bodies were only just visible. Several small recent infarcts were present, the largest measuring about 2 cc. in bulk.

Kidneys : Were of normal size. Left 130 gms. R. 125 gms. In each the capsule stripped easily leaving a surface which showed a faint fine granularity. On section the cortex appeared slightly reduced in width and the pattern a little distorted. It was of unduly red colour with poor demarcation between cortex and medulla. Consistence was firm. No lesions of the renal blood vessels were seen. Pelves were healthy.

Ureters and bladder : N.A.D.

Uterus : Showed 2 or 3 small subperitoneal myomata in addition to the usual senile atrophy.

Ovaries : Showed merely senile atrophy.

Bone Marrow : Was markedly reactive, middle of the shaft of the femur showing the fat completely replaced by fairly deep red marrow.

Abdominal Lymph Nodes : A group of several considerably enlarged lymph nodes was found on each side along the common and external iliac vessels ; they measured up to 25 x 12 x 12 mm. in size, and were homogeneous, pale grey and rather firm on section.

A group of 2 or 3 slightly enlarged lymph nodes was found at the upper border of the pancreas, which on

section/

section showed foci of old caseation.
The other abdominal lymph nodes appeared normal.

Microscopic findings :-

Lung : Sections of the cystic areas show that most of the cysts are lined by columnar epithelium ; and in the fibrous tissue deep to this there is a thinned out and patchy layer of plain muscle. The cysts therefore appear to be formed from very greatly dilated bronchi or bronchioles. Those that have no epithelial lining are lined by chronic inflammatory granulation tissue - i.e. they appear infected. The masses of debris found in some of the cysts consist of solid masses of a mycelial fungus, apparently a monilia. The tissue between the cysts consists of fibrous tissue without any sign of alveoli.

The small arteries in the septa between the cysts show striking changes ; several show acute fibrinoid necrosis, predominantly of the intima, but extending also into the media ; others show a chronic endarteritis obliterans - a gross thickening of the intima by relatively acellular concentric fibrous tissue.

That part of the lung which is not grossly cystic shows in many of the interalveolar septa the laying down of hyaline acellular fibrous tissue, producing slight thickening of the septa, with obliteration of capillaries so that the septa tend to become quite avascular. Some of these septa are breaking down, to form emphysema-like spaces (but the hyaline thickening of the septa is of course quite unlike emphysema); these spaces show no sign of columnar or cubical epithelium ; and appear therefore of different nature from the large cysts. In addition to the fine alveolar septal fibrosis there are also occasional coarser focal areas of a rather lymphocyte and plasma-cell infiltration. One of these foci of fibrosis shows a collection of peculiar cells - large cells whose cytoplasm is hyaline, and very eosinophil, the nucleus being pyknotic and pushed to one side ; sometimes the cytoplasm is lobulated, suggesting a collection of inclusion bodies of the " Russell body " type of plasma cells. Identifiable plasma cells are however not frequent. The nature of these cells is not clear. This area of the lung also shows arterial changes as in the cystic parts, but of lesser frequency - acute fibrinoid necrosis and a chronic stenosing endarteritis.

Skin : Sections from index finger pulp, calf and abdomen all showed similar changes : a thickening of the dermis as a whole, and of the individual collagen fibres ; a slight diffuse diminution in (but not disappearance of) elastic tissues ; atrophy of sebaceous glands (but slight if any atrophy of sweat glands); slight atrophy of the epidermis, with flattening of the rete pegs ; diffuse hyperkeratosis (especially in the section from abdomen); and/

and oedema and a patchy acellular collagenous fibrosis of the subcutaneous fat - most marked in the section from calf where the fat cells show atrophy and have apparently previously undergone focal necrosis, leaving a residue of foci of foamy histiocytes and an occasional giant cell grouped round empty spaces ; a small focus of calcification was seen in the immediately subcutaneous fat in this section from calf - calcium deposition in a patch of oedematous acellular fibrous tissue in the midst of the atrophic oedematous fat. No abnormality of the vessels of the skin was seen, apart from a single small arteriole in the finger section which showed a plug of granular thrombus, not completely occluding, attached to the wall and covered by endothelium.

Skeletal Muscle (Figs. 146 and 168) Sections from flexor carpi ulnaris and from gastrocnemius show a similar picture : many muscle fibres show uniform atrophy, sometimes very marked ; with considerable proliferation of sarcolemmal nuclei ; an occasional fibre shows patchy hyaline degeneration. There is a focal infiltration by lymphocytes, occasionally forming considerable dense nodular accumulations. Most of the blood vessels appear normal ; but a few arterioles show hypertrophy of the muscle coat, while others show a very cellular intimal fibrosis ; no necrosis or thrombosis.

Thyroid gland : Shows marked diffuse atrophy and fibrosis, of a degree sufficient to suggest myxoedema. In many acini the colloid appears inspissated ; sometimes these inspissated masses are surrounded by " foreign body " giant cells, the acinar epithelium having disappeared. No vascular abnormalities are seen.

Kidney : Shows a mild degree of arteriolosclerosis affecting mainly the interlobular arterioles which show intimal fibrosis, only slight hyalinisation of afferent arterioles. The parenchyma shows small focal patches of atrophy and fibrosis, presumably due to the arteriolosclerosis. No other abnormalities seen. No acute arteriolar lesions.

Heart : (L. ventricular myocardium): Shows an occasional small patch of fibrosis. The arterioles show a very definite hypertrophy of the media ; no acute changes. The larger coronary arteries on the surface show a mild to moderate atherosclerosis.

Spleen : The presence of recent infarction is confirmed. No responsible arterial blockage is found. No degenerative or necrotic changes are seen in the vessels ; there is indeed a striking absence of the hyalinosis of arterioles so common in the spleen. There is marked chronic venous congestion.

Liver : Shows only mild chronic venous congestion. Vessels appear normal.

Bone Marrow : (Middle of femur) : is markedly hyperplastic - predominantly a normoblastic reaction.

Lymph nodes : (1) : Para-aortic : a moderately enlarged/

enlarged lymph node ; but it shows no histological abnormality.

(2) Mesenteric : N.A.D.

(3) Suprapancreatic : shows extensive old caseation : no sign of active tubercle.

Oesophagus, Small intestine, large intestine : N.A.D. No atrophy, no fibrosis, no vascular changes.

Pancreas, Hypophysis, Ovary, Brain (sections of cortex and basal ganglia) : N.A.D.

Pathological diagnosis :-

Acrosclerosis.
Cystic disease of lungs. Necrotising pulmonary arteritis and endarteritis obliterans.
Sclerodermal changes in skin ; subcutaneous calcinosis.
Atrophy of limb muscles.
Atrophy and fibrosis of thyroid gland.
Renal arteriolosclerosis.
Hypertrophy of heart - both right and left ventricles.
Myocardial fibrosis.
Infarction of spleen.
Congestive heart failure - chronic venous congestion of liver and spleen, and pleural, pericardial and peritoneal effusions.

Case 538.

F aged 41. Ref :- PM 47/48

Twenty one years history of Raynaud's phenomenon with gradual loss of power in hands. Death from long-standing chronic venous congestion. Complicating healed rheumatic mitral disease. Muscle tissue obtained from rectus abdominis, pectoralis major, diaphragm (Fig. 157).

Cases 535, 536 and 539.

Biopsies were taken from individual muscles in each of these cases.

POLYARTERITIS NODOSA.

SECTION I.

Case 540.

Andrew W. aged 24.
Admitted 13.2.47, to Royal Infirmary, Ward 22.
Died 28.4.47.
Autopsy 29.4.47 by Professor A.C.P. Campbell (PM. 208/47).

Abstract of Case Notes :- Admitted 13.2.47 : Diagnosis : a typical acute rheumatism. No response to salicylate, sulphamides or penicillin : Developed multiple polyneuritis with transient paresis including (R) lower neurone facial palsy.

Albuminuria/

Albuminuria, hypertension, palpable nerve trunks. Gross wasting. Little or no response to protein shock therapy. Died quite suddenly - clinically suggests cerebral vascular thrombosis.

Macroscopic findings :-

Post mortem performed the day after death. The body was that of a young man of average height and slender build, showing great wasting, especially marked in the muscles of the lower limbs. No oedema. The skin was pale. There was no jaundice and no rashes. Small, firm, subcutaneous nodules either round or more commonly oval were seen and felt over the neck and shoulders and abdomen, sparsely distributed ; in all about 15 could be found. On reflecting the skin these were seen as grey-white nodular swellings 1 to 3 mm. in diameter occurring on the course of small, subcutaneous vessels. Some at least appeared to be on small veins. In most cases no lumen can be seen on cross section.

Skeletal Muscles : Occasional similar nodules were seen on the vessels in the fascial sheaths of pectoralis major and rectus abdominus. None were seen within these muscles or in the quadriceps or calf muscles.

Peripheral Nerves : Right ulnar, right sciatic, right common peroneal and left superficial peroneal were excised for examination. They showed no naked eye abnormality.

Head : Skull, dura and venous sinuses : N.A.D.

BRAIN : Showed slight general swelling indicated by gyral flattening of both hemispheres. The pia-arachnoid and superficial vessels appeared healthy. Brain was sent uncut to Neuro-Pathology Department.

Spine : Showed no naked eye abnormality. It was also sent uncut to the Neuro-Path. Department.

Mouth : Tongue and pharynx : N.A.D.

Tonsils : Were small, pale and healthy.

Neck & Thorax : Trachea, oesophagus and thyroid gland : Showed no abnormalities. No enlargement of the cervical lymph nodes.

Pericardial sac : Contained the usual few cc. of clear free fluid. No adhesions.

Heart 370 gms. Normal in size and shape. Pericardium appeared healthy. The coronary vessels showed several (in all 4 or 5) white fusiform nodular thickenings similar to those already described, on the course of the smaller branches. The major branches appeared normal. They showed no atheroma. There was no dilatation of any of the chambers of the heart. The left ventricle showed slight hypertrophy. Myocardium was slightly pale, but uniform in appearance and of normal firm consistence. No focal lesions were seen. The tricuspid valve admitted 3 fingers and the mitral 2 fingers. Valve cusps and mural endocardium appeared healthy. There was no obvious sign of previous rheumatic lesions.

Aorta : Appeared healthy (only an occasional trivial fleck of atheroma). Ductus arteriosus closed.

Pleural/

Pleural sacs : No free fluid. Localised delicate fibrous adhesions at both apices.

Lungs : Were of normal weight and volume, L. 430 gms. R 510 gms. The pleura was healthy apart from the above noted adhesions. On section both lungs showed merely a moderate basal congestion. There was no consolidation, no haemorrhage and no sign of arterial lesions. Mediastinal lymph glands : N.A.D.

Abdomen : No free fluid. Peritoneum healthy. Occasional nodular swellings as above described were seen on subperitoneal vessels. The lesser omentum, mesentery and the transverse meso-colon ; all showed numerous nodules on the course of the vessels, affecting arterioles of very fine, almost hair-like calibre as a rule, considerably less than 1 mm. The nodules were up to 3 mm. in diameter. Occasional nodules showed local haemorrhage surrounding them.

Stomach, duodenum, small and large intestine : All showed fairly frequent similar nodules, sub-peritoneally and within the thickness of the wall. None were visible on the mucosal surface. There were no infarcts or obvious haemorrhages visible within the bowel wall, nor did the contents appear blood stained.

Liver : Size normal. Weight 2020 gms. Surface smooth. On section very occasional nodular, arterial thickenings were seen, some showing dilatation and grey-brown thrombosis at the site of thickening. Occasional small areas of deep red haemorrhagic appearance indicating small infarcts were present. The lobular marking was rather accentuated with dark centres and pale peripheries suggesting a mixture of mild chronic venous congestion and cloudy swelling. The consistence was slightly softened.

Gall bladder and bile ducts : N.A.D.

Pancreas : No arterial lesions were seen. One small area of fat necrosis 4 or 5 mm. in diameter was found, probably an infarct secondary to a focus of arteritis.

Suprarenals : nil abnormal.

Spleen : 170 gms. Capsule wrinkled and healthy. On section pulp was of uniform, pale grey red colour. The Malpighian bodies were invisible. One small arterial nodule was seen, but no infarcts were found. The consistence was moderately softened.

Kidneys : L 260 gms. R 250 gms. Were moderately enlarged. In each the capsule stripped easily leaving a surface which was smooth generally but sparsely pitted by a few slightly depressed areas, some of which showed a central yellow patch indicating moderately recent infarcts. The surface was a pale grey red colour, profusely studded with small petechiae. On section the cortex was considerably swollen, pale grey red in colour and studded with petechiae ; contrasting sharply with the dark red medulla. The consistence was slightly softened. Numerous arterial nodules were seen mainly on arcuate and interlobular arteries. Some showed no obvious lumen on section, being uniformly grey white throughout, while others were dilated and filled/

filled with thrombus. One pea-sized aneurysm was present. None of the lesions showed brown pigmentation suggestive of old haemorrhage or thrombosis. Occasional small infarcts, yellow with a red periphery, were present throughout the cortex, up to a few mm. in diameter. They were of varying ages, some being slightly depressed but none appearing sufficiently scarred to indicate an age of more than perhaps 2 months.

Ureters, bladder and prostate : N.A.D.

Abdominal lymph nodes : N.A.D.

Bone Marrow : Middle of the shaft of the femur showed a considerable hyperplasia, the fatty marrow being largely replaced by dull red marrow.

The larger arteries throughout the body appeared everywhere normal. The lesions were confined to the small arteries (and probably some small veins). The renal arcuate arteries were the largest seen to be involved.

Microscopic findings :-

Focal arteritis was found in sections of the following organs : small intestine, mesentery, kidney, pancreas, suprarenal, liver, skin and skeletal muscle (pectoral, quadriceps and gastrocnemius). The lesion affects small arteries for the most part ; in most organs the arterioles appear unaffected, exceptions being kidney, liver, pancreas and suprarenal.

The foci of arteritis vary in age ; but most appear subacute or acute i.e. they show extensive fibrinoid necrosis of intima and media, usually affecting the whole circumference, but sometimes affecting only a segment of it ; the adventitia is grossly thickened by a granulomatous inflammatory reaction - brisk infiltration by polymorphs, plasma cells, histiocytes and a few (surprisingly few), eosinophils, proliferation of fibroblasts and new capillaries, and early collagenous fibre formation ; sometimes this granulomatous adventitia shows foci of almost caseous necrosis. In many cases the lumen of the vessel is still patent ; but sometimes it is occluded by thrombus. A few older lesions are seen, showing a cellular intimal and adventitial fibrosis, with disappearance and fibrous replacement of a varying amount of media and internal elastic lamina. These older healing foci would be compatible with an age of 2 to 3 months.

None of the affected vessels can be identified as veins ; but the destruction of the vessel wall is often so marked as to make it impossible to eliminate a vein.

Small intestine - arteritis +++. No sign of infarction or general inflammatory reaction.

Mesenteric lymph node : N.A.D.

Kidney - Arteritis +++. Several small recent infarcts seen. Fairly numerous afferent arterioles show acute fibrinoid necrosis (identical with that in malignant hypertension), and many glomeruli show damage varying in acuteness - fibrinoid necrosis of a part of the tuft, fibrinous exudate in the space, capsular/

capsular adhesions, hyalinisation of part or whole of the tuft. Related tubules are sometimes packed with R.B.C.s. No arteriolar hyalinosis seen.

Pancreas - Arteritis +. Occasional small areas of acute infarction seen. A few arterioles show fibrinoid necrosis.

Suprarenal - Arteritis ++. One small infarct of cortex seen. Occasional arteriolonecrosis.

Liver - Arteritis +. Occasional arteriolonecrosis. The liver cells appear undamaged ; no infarcts are included in the section.

Spleen : The central arterioles show a mild hyalinosis - an almost normal finding probably unrelated to the present illness. There is no arteritis or arteriolonecrosis in the section. The Malpighian bodies are normal. The pulp is less congested than normal, and shows a slight polymorph infiltration.

Skeletal Muscle (Figs. 167 and 172). Apart from arteritis (which is not as frequent as in some of the other organs) some areas of muscle show a rather diffuse moderate atrophy of fibres, with increase (both condensation and proliferation) of sarcolemmal nuclei - presumably an ischaemia atrophy from vascular occlusion.

Skin (Fig. 127). Confirms arteritis of an immediately subcutaneous artery. The skin itself shows no abnormality.

Myocardium : N.A.D. Arteries and arterioles in the section appear normal. No evidence of rheumatic or other myocarditis.

Lung - No arteritis seen (2 sections). There is well-marked chronic venous congestion, with many heart failure cells and some oedema. No pneumonia or bronchitis seen.

Oesophagus - Shows a very brisk acute or subacute oesophagitis, congestion, oedema and copious polymorph and plasma cell infiltration of the mucosa and submucosa, with superficial epithelial desquamation. This does not appear to be secondary to vascular damage ; the vessels in the section appear healthy.

Bone Marrow (mid femur): Shows a considerable hyperplasia, of mixed normoblastic-myelocytic type. No arteritis seen in the section. No noticeable increase in eosinophils.

Hypophysis, Tonsil & Synovia of knee joint : N.A.D. No arteritis seen.

Bacteriological Report : Heart Blood : no growth has been obtained.

Pathological diagnosis :-

Polyarteritis nodosa affecting the following vessels -

Subcutaneous, muscular, subperitoneal, renal coronary, mesenteric, gastric, intestinal, hepatic, splenic, pancreatic, suprarenal and probably others.

Infarct of -

Kidney, liver, pancreas and suprarenal.

Chronic/

Chronic venous congestion of liver and lung.
Hyperplasia of bone marrow.
Acute oesophagitis.
Arteriolonecrosis in kidney, liver, pancreas, and suprarenal.

Dr. Blackwood's Report on brain after fixation :-

On section a massive recent haemorrhage was present in the right cerebellar hemisphere. Small perivascular haemorrhages were present in the pons on the left side. The cerebellar haemorrhage nearby reached the surface on the inferior aspect of the lobe and had ruptured into the 4th. ventricle so that a little blood was present in all the ventricles.

Microscopically : Both sciatic and common peroneal nerves show extensive demyelination.

Foci of periarteritis nodosa where seen in the following situations - retina (acute), sciatic (Old) and peroneal (old) nerves, central cortex (acute, perforating cortical arterioles), towards the edge of the haemorrhage in the cerebellum where two small arteries are now disintegrated. In relation to the cortical vessels there is focal ischaemic degeneration of cerebral tissue. It was not present in the sections examined of choroid plexus, frontal cortex, pons (though there are terminal capillary haemorrhages here) occipital cortex, basal ganglia.

Anatomical diagnosis : Polyarteritis nodosa.

Case 541.

M aged 29. Ref :- 317/50.

Polyarteritis nodosa affecting kidneys, heart, oesophagus, intestine, liver, pancreas, left suprarenal, muscles and nerves. Synovial tissue obtained from shoulder and knee, muscle from rectus abdominis, pectoralis major, diaphragm and quadriceps and nerve from brachial plexus and femoral nerve.

Case 542.

M aged 21. Ref :- PM 504/51

Polyarteritis nodosa affecting heart, kidneys, suprarenals, liver, skin, muscles, nerves and synovial tissue. Synovial tissue obtained from both knees (Fig. 38), muscle from pectoralis major, diaphragm and adductor margins and nerve from both femoral nerves.

SECTION II.

Cases 541 and 542 were used here.

SECTION III.

Cases 540 and 542 were used here, also

Case 543.

M/

M aged 40. Ref :- MHB 6522 and 6594.
Pneumonia followed in two months by joint and muscle pains, pyrexia, albuminuria and hypertension. Transient subcutaneous nodules, the one studied being from the elbow region.

SECTION IV.

Cases 540, 541, and 543 were used here, also Cases 544 to 548 (Ref:- PM. 451/42, EHA 530, EHB 2925, PM. 511/46 and PM. 128/49) from which one or more muscles were studied either at biopsy or autopsy, the diagnosis being confirmed in all cases by the presence of lesions elsewhere.

SECTION V.

Cases 541, 544, 545 and 548 were used here, also Cases 549 to 550 (Ref:- PM 142/50 and PM. 327/50) from each of which six blocks from brachial plexus and femoral nerve were examined at autopsy, the diagnosis being confirmed in all cases by the presence of lesions elsewhere.

SECTION VI.

Lesions in coronary vessels were studied in Cases 541, 542, 544, 545 (described above) and in Cases 551 to 553 (Refs :- PM. 116/48, 455/50 and MHA 3407) in all of which typical lesions were present.

NON-RHEUMATIC DISEASES.

SECTION I.

1. Cases of non-specific synovitis :-

Case	Ref:	
558	XXVII/548	synovitis right elbow
559	XXXII/718	synovitis right knee
560	XXXIII/723	synovitis knee
561	XXXVIII/332	post-traumatic synovitis wrist
562	XLII/69	recurrent synovitis knee
563	(XLII/413	post-traumatic synovitis
	(XLIII/80	knee
564	XLII/416	recurrent effusion knee
565	XLIII/535	synovitis left knee
566	XLIV/1074	synovitis knee
567	XLVI/410	synovitis knee
568	XLVI/685	synovitis with effusion right knee
569	XLVII/903	post-traumatic arthritis knee
570	XLVIII/37	effusion knee
571	139	effusion knee
572	190	effusion knee
573/		

573	XLIX/221	effusion sterno-clavicular joint
574	552	synovitis knee
575	1122	recurrent synovitis R.knee
576	LIII/7	synovitis knee
577	536	hyperplastic synovitis knee
578	LIV/39	recurrent synovitis R.knee
579	1446	effusion left knee
580	2512	synovitis with effusion left knee
581	2649	synovitis right sterno-clavicular joint.
582	2700	chronic synovitis L. fourth prox. interphalangeal joint
583	MHB 1473	synovitis left elbow
584	3734	recurrent synovitis R.knee
585	EHB 180	post-traumatic synovitis right knee
586	764	post-traumatic haemorrhagic synovitis knee
587	803	chronic synovitis R. knee
588	824	post-traumatic hyperplastic synovitis knee
589	857	synovitis left knee
590	901	synovitis left knee
591	1008	villous arthritis knee
592	1260	synovitis knee
593	1492	hyperplastic synovitis knee
594	1702	effusion knee
595	1241	chronic synovitis
596	3204	synovitis left knee
597	3307	post-traumatic synovitis right knee

Case 598.

M aged 30. Ref :- EHB 3309

Mono-articular arthritis of right knee of 8 months' duration. No radiological evidence of destruction of cartilage or bone. At operation, synovial tissue was grossly thickened and brick red in colour. Histological appearances identical with those of rheumatoid arthritis (Fig. 39). No involvement of other joints in the year following biopsy.

2. Cases of loose-body in the knee :-

Cases 599 to 603 (Ref:- XXIV/70, XL/541, XLV/601, XLIX/477, LII/5, MHB 3724, EHB 115).

3. Cases of septic arthritis :-

Case	Ref :	
606	XXVI/686	chronic arthritis knee after fractured patella
607	XXXVIII/670	septic arthritis meta-tarso-phalangeal joint
608	XLI/19	streptococcal arthritis knee
609	LIV/272	septic arthritis fifth right metatarsophalangeal joint

610/

610	MHB 857	septic arthritis knee
611	2227	septic arthritis ankle
612	PM 333/47	subacute streptococcal synovitis knee

4. Cases of osteochondritis of knee :-

Cases 613 to 616 (Ref:- XLII/126, LII/1849, LV/712, EHB 1178).

5. Cases of torn menisci of knee :-

Cases 617 to 644 (Ref:- XXX/191, XXXV/14, XXXVII/102, XL/689, XLII/714, XLV/92, XLVIII/977, LIII/1287, 1372, 2338 & 2416, LIV/1224, 1563, 2034 and 2386, LV/79, MHB 3399, 4038, 5980, 6789, EHB 29, 70, 1122, 1162, 1701, 1751, 1864, 2972).

6. Cases of cysts of menisci of knee :-

Cases 645 to 663 (Ref :- XXIV/708, XLIII/287, XLIV/701, XLVIII/1021, L/803, LI/1052 and 1080, LII/1095, 1172 and 1355, LIV/1514, LV/714, MHB 7850, EHB 78, 175, 834, 1177, 1649, 3379.

7. Cases of haemophilia affecting knee :-

Cases 664 to 665 (Ref:- PM 316/49 and 84/50).

8. Cases of tuberculous arthritis :-

a) of the elbow - Cases 667, 682 & 696 (Ref :- XXVI/340, LIII/1481, EHB 1704).
b) of the hip - Cases 668 to 670 (Ref:- XXVII/139, XXX/736, XXXII/6373)
c) of the knee - Cases 666, 671 to 681, 683 to 695, 697 to 700 (Ref:- XXV/550, XXXII/729, XXXIII/19, XXXVIII/58, XLII/313, XLVII/1131, XLIX/173, L/1246, LI/502, 906, 1668, LII/1001, LIII/2153, LIV/552, 718, 1170, 1634, 1738, MHB 1477, 4678, EHB 207, 532, 660, 730, 1213, 2739, MHA 2569, 2743).

9. Cases of syphilitic arthritis :-

Case 701 Ref :- MHB 3973 sterno-clavicular joint
702 IB 5144 knee

10. Cases of non-specific bursitis :-

a) olecranon bursa - Cases 711, 714, 719, 720, 724, 735, 758, 776, 778, 784, 797, 810 and 816 (Ref:- XXIX/110, 673, XXXII/943, 1107, XXXV/470, XXXVIII/258, XLV 111/539, LI/1270, 1341, LIII/1681, MHB 1227, EHB 637, MHA 2309).
b) around wrist - Cases 739, 741, 756 and 815 (Ref:- XXXIX/906, XL/220, XLVII/210, EHB 3365).
c) around knee - Cases 703, 705-707, 709, 710, 712, 713, 715, 717, 718, 722, 725, 727, 728-730, 732, 733, 737, 740, 743-745, 747-751, 755, 757, 759, 762, 764-767, 770-772, 775, 779, 785, 788, 789, 791, 794-796, 800, 803-808, 811-813. (Ref:/

(Ref:- XXVII/183, 423, 433, 554, XXVIII/375, 728, XXIX/206, 266, XXXII/249, XXXIII/450, 791, XXXIV/140, XXXV/597, XXXVI/742, XXXVII/177, 541, 824, 1054, XXXVIII/145, 646, XL/34, XLIII/176, 534, 676, XLIV/999, XLV/456, 488, 1027, 1188, XLVI/1071, XLVII/555, XLVIII/876, XLIX/269, L/388, 564, 950, 1058, 1420, LI/226, 281, 1225, 2028, LIII/2020, LIV/387, 555, 725, LV/147, 474, MHB 864, 7881, EHB 56, 71, 85, 528, 603, 604, 866, 1097, 1663).

d) around ankle and foot - Cases 704, 708, 716, 731, 736, 751-753, 760, 761, 773, 781, 791, 794, 798, 801, 802, 809 (Ref:- XXVII/292, 658, XXXIII/351, XXXVII/928, XXXVIII/606, XLVI/304, 375, 387, XLVIII/1123, XLIX/216, LI/861, LII/1715, LIV/662, 893, MHB 5037, EHB 16, 22, 606).

4) other sites -

Case	Ref :	
721	XXXIV/20	ischial tuberosity
723	XXXIV/241	deep to ilio-tibial tract
734	XXXVIII/200	tibial tuberosity
742	XLII/692	over tibia
763	XLIX/1294	calf
774	LI/885	over tibia
782	LII/2093	over tibia
783	LII/2207	subsartorial
786	LIII/2191	amputation stump forearm
793	LIV/820	subtrochanteric
799	MHB 6424	subacromial
814	EHB 2908	right shoulder

f) Site unknown - Cases 726, 738, 746 and 780 (Ref:- XXXV/776, XXXVIII/808, XLIII/866, LII/42).

11. Cases of tuberculous bursitis :-

817	XXIX/193	trochanteric
818	XXXIII/1199	wrist
819	XL/457	prepatellar
820	XLII/817	ischial
821	LI/942	trochanteric
822	EHB 1143	prepatellar

12. Cases of non-specific tenosynovitis :-

a) extensor tendons of wrist - Cases 823, 824, 827, 829-832, 835, 840-842, 844, 845, 847, 848, 851, 857, 859, 860, 865-868, 870, 872, 873, 875, 877-880, 882, 884-886, 888-895, 897 (Ref:- XXVII/258, XXVIII/3, XXXIII/1110, XXXIV/76, 488, XXV/25, 679, XXXVI/592, XXXVII/757, XXXVIII/33, 658, 877, 979, XXXIX/251, XLI/474, XLV/159, XLVII/1314, XLVII/175, LII/80, 1269, 1446, 1742, 1900, LIII/80, 243, 1223, 2183, 2485, LIV/121, 269, 2339, LV/131, 205, 262, 551, 747, 815, MHB 790, 8552, EHB 64, 729, 996, 1419.

b) extensor pollicis longus - Cases 828, 846, 854, 856, 869, 881, 883, 887 (Ref:- XXXIV/63, XXXVIII/949, XLII/485, XLIV/606, LII/1868, LIV/80, 2278, LV/470).

c/

c) palm of hand :- Cases 826, 836, 850, 861 (Ref:- XXXIII/1080, XXXVII/189, XXXIX/801, XLIX/70).

d) other sites

Case	Ref :	
825	XXXIII/325	tibialis anterior
833	XXXVI/148	extensor of finger
838	XXXVII/550	peroneus longus
839	XXXVII/589	extensor of finger
843	XXXVIII/453	flexor of wrist
849	XXXIX/329	flexor pollicis longus
852	XLI/775	Achilles tendon
853	XLII/467	peroneus longus
855	XLIV/339	extensor of finger
858	XLV/994	extensor offinger
863	LI/691	flexor of wrist
864	LI/1193	extensor hallncis longus
876	LIII/1629	extensor hallucis longus
896	EHB 1171	ankle

e) site unknown - Cases 829, 837, 862, 871, 874, 891, 897 (Ref:- XXXVI/319, XXXVII/231, L/961, LII/2313, LIII/468, MHB 790, EHB 1419).

13. Cases of tuberculous tenosynovitis :-

a) extensor tendons of wrist - Cases 900, 902, 905, 915, 916, 920, 922 (Ref:- XXXIV/326, XXXV/672, XXXVII/241, L/1380, LI/996, LIII/1207, 1411).

b) flexor tendons of wrist - Cases 901, 906-908, 914 (Ref:- XXXV/47, XXXVII/71, XL/678, XLII/496, XLIX/267.)

c) extensor tendons of fingers - Cases 898, 899, 912, 918, 921, 923, 924 (Ref:- XXX/594, XXXIII/477, XLVIII/756, LII/2051, LIII/1393, MHB 761, EHB 894).

d) flexor tendons of fingers (compound palmar ganglion) - Cases 904, 909, -911, 913, 917 (Ref:- XXXVII/168, XLV/166, 167, XLVII/794, XLVIII/1012, LI/1907).

e) site unknown - Case 903 (Ref:- XXXVI/320).

14. Case of amyloidosis ofleft knee :-

Case 925.

Christina W. aged 71.
Admitted 19.7.48 to Northern General Hospital, Ward 4.
Died 21.7.48.
Autopsy 22.7.48 by the writer.

Abstract of Case Notes :- This woman was admitted on 19.7.48 with a history of general weakness of 18 months duration, and pains in her knees, hands, elbows, shoulders and feet, which started in her knees in April 1948, and gradually involved the other joints. Before this time she had no joint trouble whatsoever/

whatsoever but, from time to time, had vague muscular pains. Her appetite was poor with occasional vomiting. Bowels constipated, at times stool dark. Increased frequency of micturition for two months. Two weeks before admission she noticed that her eyes were yellow.

On admission : Pale, thin, starved elderly woman. No jaundice. No enlarged glands. Appearances of active rheumatoid arthritis in wrists and hands, all small joints being involved. In addition painful limited movement of both shoulders, both elbows and both knees were present. There was also tenderness over the lumbar spine and* C.V.S. Pulse regular. B.P. 140/80. Heart nil. Resp. Crepitations at both lung bases particularly right side. Alimentary : Tongue - brown, dry and furred. Gums infected. Nil abnormal on abdominal examination. C.N.S. - n.a.d. Blood : Hb. 56% ; R.B.C. 2.73 m. W.B.C. 7,600. B.S.R. 112 P.C.V. 28%. Film - cells well filled with little variation in size. Differential - Neutro 52% Eosin 1%. Baso 1% Lymph. 32%. Monos. 2%. Urine - albumin plus with a few pus cells. Investigations : Not yet back. Plasma uric acid B.U.N.
Plasma proteins 20.7.48 - alb. 3.20 glob. 1.80
Blood culture 20.7.48 - no growth.

On 20.7.48 she developed a temperature of 104 with increased respiration. There was no examination of the chest, an area of bronchial breathing in the left lower lobe. W.B.C. 5,800. Despite intensive penicillin therapy, her temperature continued rising and she died at 6.20 p.m.

* limited movement of ankle and small joints of feet.

Macroscopic findings :-

The body was that of a senile woman, of poor nutrition and with wasted limbs. The joints of the limbs were swollen, the knee joints being most affected and the others much less severely. There was neither jaundice nor oedema.

Head : Brain and meninges showed no macroscopical abnormality. There was very slight atheroma of the cerebral vessels.

Mouth and pharynx were healthy.

Neck and Thorax : Thyroid was considerably reduced in size, both lobes containing a considerable amount of fibrous tissue.

Larynx, trachea and main bronchi were healthy.

Pleural sacs contained a normal amount of serous fluid.

Lungs were of average size. The posterior parts and lower lobes were congested and oedematous, but neither bronchitis nor pneumonia were detected.

Pericardial sac contained approximately 10 cc. of serous fluid. A few "milk" spots were present in the epicardium on the anterior surface of the left ventricle.

Coronary vessels showed a moderate degree of eccentric atheromatous thickening.

Heart/

Heart was slightly above average size. Right auricle and ventricle were not dilated or hypertrophied. Tricuspid orifice admitted four fingers : the cusps were healthy. Pulmonary valve and artery were healthy. Left auricle and mitral valve were healthy. Left ventricle was slightly hypertrophied and dilated. The myocardium of both ventricles was pale and flabby. Aortic valve was healthy.

Aorta showed considerable atheroma with ulceration of some of the plaques in the arch. Plaques in the first part of the aorta extended to the base of the aortic cusps.

Oesophagus was healthy.

Abdomen : Peritoneal sac was healthy.

Stomach and duodenum were healthy.

In the jejunum there were numerous diverticula which commenced near the duodenojejunal flexure and involved approximately 3 ft. of the intestine. They varied in size, some having a capacity of approx. 5 cc. They tended to a spherical shape with a narrow neck and many contained solid masses of food and faecal material. They showed no ulceration. They were situated close to the mesenteric attachment.

Ileum and the greater part of the large intestine were healthy. In the pelvic colon there were numerous shallow pockets in the wall representing early diverticula.

Spleen was of average size, rather friable with red-purple pulp.

Liver and biliary passages showed no abnormality.

Pancreas and adrenal glands appeared to be normal.

Kidneys were slightly below average size. The cortex showed slight irregularity and was slightly reduced in depth. Both cortex and medulla were very pale. The arcuate arteries were thick-walled.

Renal pelves, urinary passages and genital organs showed no abnormality.

Knee Joints : Left knee joint was removed intact.

Right knee joint was opened. The synovial tissue was thickened and it was congested in proximity to its attachment to the anterior aspect of the tibia. The articular surfaces were roughened centrally and the cartilage was thin.

Bone Marrow : Reddish brown marrow was removed from the distal end of the femur for microscopical examination.

Addendum to naked eye Report : Left knee : The synovial membrane is generally hyperplastic with many villi and much of it is apparently necrotic. After study of the microscopic material , an iodine test was carried out and all this material gave the dark brown reaction characteristic of amyloid. Occasional areas of haemorrhage are present in the membrane. Bursae, filled with similar material are present between the tendon of popliteus and the medial/

medial meniscus, and beneath the tendon of adductor magnus.

The articular cartilage of the patellar facet of the femur is thin and roughened, much of its surface being covered by connective tissue. The femoral condyles show a lesser degree of the same change. Considerable osteophytic lipping is seen on the margin of the femoral articular cartilage. On the tibia slight changes are seen of a similar nature to those on the patellar facet of the femur and the free edges of the menisci are white and friable. Changes of a more advanced degree are seen on the articular facets of the patella - marked degeneration of cartilage, much pannus and some lipping.

Microscopic findings :-

Heart : Blocks were taken from right auricle, right ventricle, left ventricle (2), mitral valve with adjacent auricle and ventricle, and inter-ventricular septum, and single sections from each examined.

The pericardium over the left auricle is diffusely thickened by a surface layer of dense fibrous tissue, deep to which are dense foci of lymphocytes with small numbers of plasma cells and histiocytes. Elsewhere it is healthy. In the left ventricular myocardium near the mitral valve, a few small patches of fibrosis are seen mostly affecting the adventitia of vessels and adjacent muscle fibres. The endocardium is everywhere healthy. Atheromatous changes are seen in some branches of coronary arteries and have caused moderate narrowing of the lumen.

Lungs : marked congestion throughout the section, with oedema in most of it, the alveolar fluid containing large numbers of polymorphs and some fibrin. In unaffected areas, alveoli are widely distended, sometimes with break-down of their walls to form large air-spaces.

Pancreas : N.A.D.

Kidneys : Diffuse fibrosis with atrophy of tubules many of which contain hyaline, granular or cellular casts, and some contain desquamated cells or blood. Very occasional medullary tubules contain small numbers of polymorphs. Accompanying the fibrosis is focal round-cell infiltration. Glomeruli are practically unaffected, only an occasional one showing fibrosis. There is diffuse hyperplastic sclerosis of small arteries and many arterioles in the cortex. Venules are frequently congested. The pelvis shows desquamation of epithelium, patchy oedema and fibrosis and occasionally slight round cell infiltration. The appearances are those of chronic pyelonephritis.

Spleen : Small tags of fibrous tissue infiltrated with round cells are attached to the capsule. Malpighian corpuscles are greatly reduced in number and size, with central arterioles unduly thick-walled and /

and hyaline. The red pulp is moderately congested and contains very large quantities of haemosiderin.

Bone marrow : normoblastic.

Skeletal Muscle : Blocks were taken from rectus abdominis, pectoralis major, diaphragm, deltoid, psoas, quadriceps, gastrocnemius, adductor magnus and tongue (2).

A single small endomysial focus of lymphocytes and histiocytes is present in the section from gastrocnemius. This and other muscles, such as rectus pectoral and quadriceps show varying degrees of atrophy but the striking feature is the presence in the tongue, diaphragm and deltoid of patches of varying size of irregularly staining eosinophilic material, sometimes granular and sometimes homogeneous. These patches are sometimes localised as in deltoid and are up to 2 mm. in longest diameter, but elsewhere, as in the diaphragm there is diffuse infiltration with this material. Small numbers of irregular mesenchymal cells are seen in it. Adjacent muscle fibres are atrophic and sometimes show hyaline change or histiocytic absorption. The walls of small vessels do not contain this material. In the tongue, there is a thick deposit beneath the epithelium with diffuse infiltration elsewhere. In frozen sections of the tongue stained with Congo Red, this material stains selectively and the tongue, like the synovial membrane stained dark brown with iodine in affected areas. This material is thus amyloid.

Peripheral Nerve : Six blocks from peripheral nerve were examined. No inflammatory foci are present.

Synovial membrane : (Figs. 47 and 48). Four blocks were taken from the synovial membrane of the left knee, one from the medial meniscus and three from the bursae around the joint.

In none of the sections from these blocks are the features of rheumatoid arthritis seen. Instead, all of them show varying degrees of amyloid degeneration. In those parts of the membrane which appeared villous to the naked eye, the appearances are striking for many of these villi have a core of connective tissue which is oedematous and contains small numbers of lymphocytes and histiocytes but is free of amyloid. In contact with this tissue is a well defined though irregular zone of large synovial cells sometimes in several layers and outside this again is the zone of amyloid change, the tissue being considerably broken up by oedema. Elsewhere large masses of amyloid are seen, as in the deltoid, often freely infiltrated with large histiocytes and foreign body giant cells. A denser layer of amyloid is present on the surface of the meniscus.

The bursal contents are also amyloid, often in cylindrical masses up to 20-30 u. in diameter. Large histiocytes, giant cells and lymphocytes are again seen, mostly, healthy, but occasionally pyknotic. Thin fibro-fatty septa run through the amyloid and are lined by an oedematous zone containing synovial cells and amyloid material as in the joint itself.

In/

In one of the blocks from the bursa there are very many markedly congested capillaries from many of which haemorrhage has occurred.

Pathological diagnosis :-

Chronic pyelonephritis.
Uraemia
Amyloidosis of left knee and skeletal muscles.
Pulmonary oedema.

SECTION III.

1. Cases of granuloma annulare :-

Case 926 Ref :- RCP 4451/43 (Fig. 110)
Case 927 F. aged 77. Ref :- S133
Lesions on right cheek for 3 months.
Case 928 Ref :- S211
Case 929 Ref :- S 332
Case 930 F. aged 22. Ref : SD 105 and 120.
Lesions on finger for a year (Fig. 116).
Case 931 F. aged 40. Ref : SD 132
Lesion, 1 cm. in diameter on left thigh (Figs. 111 and 114).
Case 932 F aged 10. Ref : SD 371
Lesion on back of hand for many years
Case 933 F aged 6. Ref : SD 1266 (Figs. 112, 115, 117)
Lesions on palms, backs of hands and knees. Biopsy taken from palm.
Case 934 M aged 9. Ref : SD 1445
Lesions on back of right hand and on ears. Biopsy taken from hand.
Case 935 M aged 9. Ref : RHSC/B 1823 & 1838/51.
Admitted to hospital for investigation of idiopathic epilepsy of 7 years' duration. Nodules the size of melon seeds had been present beneath skin on dorsum of right hand for 6 years and on left hand for 3 years. They increased gradually in number and were intermittently painful for up to a week. On admission there were 30 nodules on the right hand and 15 on the left hand. Xrays of hands normal. BSR 3 mm. per hour (Figs. 118 and 119).

2. Cases of " rheumatoid " nodules without arthritis :-

Case 936	Ref:-	SD 1105	Text p 159
937		SD 1171	see text p 159
938			text p 157 & Fig. 126
939			text pp.157-158 & Fig.127.

3. Cases of subcutaneous gumma :-

Case 940 Ref :- PM 44/38 see text p. 167 and Fig. 134.
Case 941 see text p. 167 and Figs. 135 and 136.

4. Cases of tuberculous adenitis :-

Cases 942 - 981 (Ref:- MHB 3029, 3704, 3707, 10525 and 10526, EHB 491, 512, 524, 584, 644, 658, 669, 675, 702, 714, 746, 750, 774, 798, 1066, 1147, 1225, 1377, 1486, 1527, 1561, 1570, 1578, 1657, 1680, 1682, 1724, 1775, 1800, 2615, 2728(a), 2732, 2929 and 2990, Ely 15086/45).

5. Cases of foreign body granuloma :-

a) suture material - Cases 989, 998, 1003, 1005, 1010 (Ref :- XXXVIII/720, XLIV/198, LII/412, LIII/729, LIV/2516).

b) pencil lead - Cases 983, 984, 1000 (Ref :- XXXV/426, XXXVII/79,XLVII/1120).

c) wood - Case 982 (Ref: XXVIII/68).

d) steel - Case 988 (Ref: XXXVIII/491).

e) coal - Case 1006 (Ref: LIII/1002).

f) nature of foreign body not known - Cases 985 -987, 990-997, 999, 1001, 1002, 1004, 1007-1009, 1011 (Ref :- XXXVII/448, 790, 1043, XXXVIII/885, XL/11, 931, XLI/759, XLII/151, 637, XLIII/487, 622, XLVI/1019, LI/182, LII/74, 771, LIII/1119, 1200, LIV/774, EHB 1601.

6. Cases of inclusion dermoid cyst :- Cases 1012 - 1034 (Ref :- XXXIX/187, XLII/ 324, XLIII/654, XLIV/519, 848, XLV/55, 204, 674, XLVI/200, 464, 889, 922, 1000, 1180, XLVII/711, 868, 945, 1059, 1315, XLVIII/286, XLIX/288, LIII/543, LIV/1153.

7. Cases of traumatic nodules :- Cases 1035 and 1036 (Ref:- MHB 8617 and 7851).

8. Case of arteriosclerosis resembling rheumatoid nodule :- Case 1037 (Ref:- 1103) (Fig. 141).

SECTION IV.

Cases 925 (under Section I) and 1037 (under Section III) were used here.

In the following cases, the major pathological lesions are noted, also the number of blocks taken (in brackets). Tissue was obtained during surgical operation in those cases marked with as asterisk.

Case	Ref :-	
1038	MHB 1287	amyoplasia congenita (2)
1039	PM 182/48	subacute prostatitis, purulent cystitis ; pulmonary embolism (4)
1040	184/48	gastric ulcer, perforation, subphrenic abscess (3)
1041	195/48	tuberculosis lungs and pericardium (3)
1042	196/48	duodenal ulcer, perforation, peritonitis (3)
1043	197/48	appendicitis ; anthracosilicosis, pulmonary tuberculosis (4)
1044	198/48	duodenal ulcer, haematemesis ; pulmonary embolism (4)

1045/

1045	199/48	emphysema, tension pneumothorax (3)
1046	201/48	duodenal ulcer, perforation, peritonitis ; cystic goitre (3)
1047	202/48	carcinoma rectum : medulloblastoma (3)
1048	206/48	cholecystitis, perforation, peritonitis ; nephrosclerosis (3)
1049	209/48	lobar pneumonia, lung abscess; cirrhosis liver (4)
1050	MHA 2732	dural tears, atelectasis (2)
1051	2722	carcinoma pancreas, ulceration and perforation duodenum, peritonitis (3)
1052	2714	atelectasis (3)
1053	2731	subarachnoid haemorrhage ; atelectasis (2)
1054	2712	dural tears ; asphyxia (3)
1055	2652	poliomyelitis ; pyelitis ; pregnancy (10)
1056	LI/1725	hypertension (1)
1057	PM 466/47	toxic goitre, thyrotoxic crisis(1)
1058	356/47	lymphatic leukaemia (4)
1059	MHB 1060	congenital torticollis (1)
1060		traumatic denervation (1)
1061		traumatic denervation (1)
1062	PM 63/48	encephalitis lethargica ; pyelitis, pregnancy (3)
1063	MHA 2651	pneumonia ; purulent meningitis (3)
1064	LII/664	fibrosarcoma tibia - amputation specimen (9)
1065	PM 252/48	bronchiectasis ; shock after lobectomy (3)
1066	253/48	appendicitis, psoas, abscess ; subacute nephritis (4)
1067	254/48	chronic glomerulonephritis, uraemia (4)(Fig. 158)
1068	255/48	coronary atheroma, myocardial infarction (4)
1069	256/48	peptic ulcers, perforation, peritonitis (3)
1070	267/48	pyelonephritis ; cirrhosis liver ; emphysema (4)
1071	260/48	carcinoma cervix ; sclerosing haemangiomata lungs, spleen and liver (3)
1072	261/48	carcinoma breast (3)
1073	204/48	polyneuritis ; carcinoma bronchus ; myxoedema (4)
1074	271/48	carcinoma rectum, peritonitis (3)
1075	266/48	diverticulitis, abscess, peritonitis (4)
1076	257/48	appendicitis ; pulmonary embolism (4)
1077	268/48	miliary tuberculosis, tuberculous meningitis (4)
1078	275/48	acute liver necrosis (5)
1079	276/48	carcinoma cervix, vesico-vaginal fistula (5)
1080	284/48	myeloma ileum ; pulmonary tuberculosis (4)
1081/		

1081	278/48	traumatic subarachnoid haemorrhage (4)
1082	279/48	cirrhosis liver ; shock after operation (5)
1083	289/48	carcinoma bronchus, empyema (5)
1084	290/48	dislocation hip ; aspiration vomitus, asphyxia (4)
1085	291/48	silicosis, bronchopneumonia, empyema (5)
1086	297/48	diverticulitis, peritonitis, cellulitis (8)
1087	298/48	fractured skull, cerebral trauma (4)
1088	212/48	gastrocolic fistula, peritonitis (2)
1089	301/48	infantilism ; purulent peritonitis (6) (Fig. 162)
1090	213/48	Hodgkin's disease ; cirrhosis liver (3)
1091	303/48	myasthenia gravis, thymoma (7)
1092	314/48	progressive muscular atrophy ; bronchopneumonia (7)
1093	333/48	bronchiectasis, emphysema ; cardiac failure (4)
1094	336/48	carcinoma pancreas, subphrenic abscess (4)
1095	337/48	bilateral cerebellar infarction (5)
1096	342/48	senile hyperplasia prostate ; pancreatitis (4)
1097	344/48	senile hyperplasia prostate ; septicaemia (6)
1098	MHA 2743	bronchiectasis ; carcinoma stomach tuberculosis knee (3)
1099	PM 438/48	carcinoma bronchus (6)
1100	456/48	lymphatic leukaemia (6) (Fig.176)
1101	MHA 3082	bronchiectasis, bronchitis, bronchopneumonia (5)
1102	2652	normal 5 month foetus (5)
1103	2659	bilateral atelectasis (3)
1104	2661	gastroenteritis ; purulent otitis media (4)
1105	2662	carcinoma bronchus, bronchiectasis, pancreatitis (3)
1106	2669	dural tears ; atelectasis (3)
1107	2672	gastroenteritis ; marasmus (3)
1108	2725	carcinoma stomach (3)
1109	2800	carcinoma uterus ; miliary tuberculosis (6)
1110	2806	polycystic kidneys, uraemia (6)
1111	2809	Parkinsonism ; bronchopneumonia (4) (Fig. 144).
1112	2559	nephrosclerosis ; myocardial infarct ; bronchiectasis (3)
1113	2632	rupture of congenital cerebral aneurysm (3)
1114	2633	bronchitis, bronchopneumonia ; cardiac failure (3)
1115	2649	bronchiectasis, lung abscess (3)

1116/

1116	MHA	2569	miliary tuberculosis (2)
1117		2711	carcinoma prostate, pyonephrosis (4)
1118		2705	myocardial infarcts ; carcinoma stomach (3)
1119		2543	pyelonephritis (3)
1120		2555	nephrosclerosis ; pernicious anaemia ; carbuncle (2)
1121		2561	carcinoma bronchus ; suppurative cholangiectasis (3)
1122		2567	carcinoma prostate ; shock after operation (2)
1123		2674	meningococcal meningitis (5)
1124	LII/	1018	chondrosarcoma femur - amputation specimen (3)
1125	LII/	1113	malignant melanoma leg - amputation specimen (3)
*1126			tuberculosis ankle - amputation specimen (3)
1127	PM	494/48	carcinoma cervix (2)
1128	MHA	2743	dural tears ; atelectasis (3)
1129		2776	nephrosclerosis, cerebral haemorrhage (4)
1130		2784	pyonephrosis; myocardial infarcts (3)
1131		2790	cerebral haemorrhage ; cholecystitis (4)
1132		2792	myocardial infarct (5)
1133		2797	carcinoma bronchus, lung abscess (5)
*1134			duodenal ulcer (1)
1135	PM	166/48	bronchiectasis, emphysema, cardiac failure (3)
1136		168/48	carcinoma bile duct; renal failure (3)
1137		171/48	carcinoma prostate ; pulmonary tuberculosis (3)
1138	MHA	2781	measles; membranous gastritis ; intussusception (2)
*1139			appendicitis (1)
*1140			cholecystitis (1)
1141	MHA	2687	hydrocephalus ; amyoplasia congenita (5)
*1142			duodenal ulcer (1)
*1143			cholelithiasis (1)
1144	SMP	53/48	erythroblastosis foetalis (3) (Fig. 177)
1145	PM	159/48	carcinoma bronchus ; bronchopneumonia (3)
1146		162/48	bronchiectasis, empyema (3)
1147		164/48	duodenal ulcer ; nephrosclerosis, cerebellar infarct (3)
*1148			duodenal ulcer, perforation, subphrenic abscess (1)
*1149			appendicitis (1)
*1150			senile hyperplasia prostate (1)
*1151			bronchial cyst (1)
*1152			carcinoma kidney (1)
1153	MHA	839	emphysema, bronchopneumonia, cardiac failure (5)

1154/

1154	MHA	2987	carcinoma colon, peritonitis ; nephrosclerosis (5)
1155		2990	primary pulmonary tuberculosis, tuberculous meningitis (4)
*1156			appendicitis (1)
1157	SMP	52/48	hydrocephalus ; spina bifida (3)
1158		54/48	anencephalus (3) (Fig. 145)
1159	PM	158/48	carcinoma colon ; nephrosclerosis
1160		160/48	cerebral abscess (1)
1161		161/48	fractured femur ; nephrosderosis; bronchopneumonia (4)
1162	MHA	3007	emphysema, bronchopneumonia, cardiac failure (4)
1163		3013	fractured femur ; pyelonephritis (4)
*1164			cholecystitis (1)
1165	PM	167/48	cirrhosis liver ; myocardial fibrosis (3)
1166		165/48	nephrosclerosis, cardiac failure (3)
1167		126/48	pneumococcal sinusitis, meningitis (3)
*1168			acute pancreatitis (1)
*1169			cholecystitis (1)
1170	PM	124/48	pulmonary and adrenal tuberculosis ; Addison's disease (3) (Fig. 179)
1171		120/48	carcinoma prostate ; bronchitis (3)
1172		91/48	eclampsia(4)
1173		118/48	myocardial infarction (3)
1174		119/48	duodenal ulcer, perforation, peritonitis (4)
1175		80/48	lobar pneumonia, meningitis (10)
1176	MHA	3017	myocardial infarction (4)
1177	PM	522/48	Weil's disease (3)
1178	MHA	3021	reticulosarcoma (4)
1179		3022	poliomyelitis ; renal calculi, abscess (5)
1180		3030	benign nephrosclerosis ; carcinoma prostate (4)
1181		3032	inhaled liquor, pneumonia (4)
*1182			appendicitis (1)
1183 *			carcinoma stomach ; nephrolithiasis (1)
1184	MHA	3033	Hodgkin's disease ; pyelo-nephritis (4)
1185		3036	streptococcal septicaemia (4)
1186	PM	127/48	diabetic coma ; pulmonary tuberculosis (3)
1187		121/48	traumatic cerebral haemorrhage (3)
1188		117/48	carcinoma pancreas (3)
1189		129/48	duodenal ulcer, haematemesis ; pulmonary infarcts (4)
1190		140/48	carcinoma bronchus (3)
1191		151/48	carcinoma bile duct, suppurative cholangiectasis (3)
1192		153/48	subacute liver necrosis (3)
1193/			

1193	PM	155/48	carcinoma bronchus (4)
*1194			appendicitis (1)
*1195			duodenal ulcer (1)
*1196			appendicitis (1)
*1197			duodenal ulcer (1)
*1198			duodenal ulcer (1)
*1199			duodenal ulcer, perforation (1)
*1200			carcinoma pancreas (1)
*1201			duodenal ulcer (1)
*1202			normal individual (1)
*1203			appendicitis (1)
*1204			appendicitis (1)
*1205			carcinoma colon (1)
*1206			duodenal ulcer (1)
*1207			senile hyperplasia prostate (1)
*1208			cholecystitis (1)
*1209			gastric ulcer (1)
*1210			subacute inflammation and abscess thigh (1)
*1211			achalasia of oesophagus (1)
*1212			carcinoma stomach (1)
*1213			duodenal ulcer (1)
*1214			appendicitis (1)
*1215			cholecystitis; tuberculous lymphadenitis (1)
*1216			toxic goitre (1)
*1217			appendicitis (1)
*1218			duodenal ulcer (1)
1219	PM.	222/50	benign nephrosclerosis, cerebral haemorrhage (3)
1220	NP	545	amyotonia atrophica ; pituitary adenoma (8)
1221		591	myasthenia gravis (2)
1222		1628	amyotrophic lateral sclerosis (2)
1223		1696	Landouzy-Dejerine muscular dystrophy (2)
1224		1653	immersion foot (6)
1225		1654	immersion foot (4)
1226		1800	immersion foot (14) (Fig. 173).
1227		2046	diffuse angiomatosis (3)
1228		2159	infantile progressive muscular atrophy (4)
1229		2166	traumatic denervation (4)
1230		2173	immersion foot (1)
1231		2175	immersion foot (2)
1232		2280	congenital torticollis (4)
1233		2176	immersion foot (6)
1234		2344	congenital torticollis (2)
1235		2185	immersion foot (7)
1236		2206	immersion foot (7)
1237		2260	immersion foot and hand (17)
1238		2271	duodenal ulcer ; bronchopneumonia, lung abscesses (6)
1239		2281	Volkmann's ischaemic contracture (2)
1240		3499	myasthenia gravis, thymoma (3)
1241		3581	toxic goitre, exophthalmic ophthalmophegia (1) (Fig.164)
1242		3593	progressive muscular atrophy (1)
1243/			

1243	NP	1542	amyotenia congenita (3)
1244		2295	traumatic denervation (1)
1245		2732	ischaemia following shell wounds (1)
1246	PM	88/46	Weil's disease (1)
1247		155/46	Weil's disease (4)
1248		342/46	Weil's disease (4)
1249		570/46	Weil's disease ; duodenal ulcer ; carcinoids (3)
1250	MHB	703	avitaminosis (1)
1251		779	hypertrophy of ligamentum flavum (1)
1252		1859	hysteria (1)
1253		2249	trench foot (1)
1254		3088	tuberculous empyema ; amyloidosis (1)
1255		5842	progressive muscular atrophy (1)
1256	EHB	353	muscular dystrophy (2)
1257		470	arteriosclerosis - amputation specimen (1)
1258		321	arteriosclerosis - amputation specimen (2)
1259	PM	109/47	Weil's disease (4)
1260		440/49	Weil's disease (3)
1261	EHB	1175	semimembranosus bursitis (1)
1262		1432	malignant melanoma (1)
1263		314	thromboangiitis obliterans - amputation specimen (3)
1264		918	tenosynovitis (1)
1265		600	thromboangiitis obliterans - amputation specimen (3)
1266		601	thromboangiitis obliterans - amputation specimen (2)
1267		1069	thromboangiitis obliterans - amputation specimen (3) (Fig.181)
1268	PM	313/48	malignant neoplasm mesentery, strangulation ileum (4)
1269		272/48	carcinoma colon (5)
1270	MHB	2402	myocardial infarction (1)
1271	PM	329/48	rupture of congenital cerebral aneurysm (5)
*1272			senile hyperplasia prostate (1)
*1273			nephrolithiasis (1)
*1274			appendicitis ; cholecystitis (1)
*1275			nephrolithiasis (1)
*1276			duodenal ulcer, perforation (1)
*1277			cholecystitis (1)
*1278			nephrolithiasis (1)
*1279			diabetes mellitus ; arterio-arteriosclerosis - amputation specimen (1)
*1280			gastric ulcer (1)
*1281			appendicitis (1)
*1282			arteriosclerosis - amputation specimen (15) (~~Fig.=199~~)
1283	LIII/1571		thromboangiitis obliterans - amputation specimen (2) (Fig.199)
1284	LIII/1570		thromboangiitis obliterans - amputation specimen (2)

*1285/

*1285			diabetes mellitus : arterio-sclerosis - amputation specimen (11)
1286	PM	44/48	senile hyperplasia prostate ; pulmonary thrombosis (1)
1287		69/48	pulmonary tuberculosis, miliary tuberculosis (1)
1288		99/48	carcinoma thyroid : pulmonary embolism (1)
1289		230/48	myxoedema ; myocardial infarct (1)
1290		424/48	parathyroid hyperplasia (1)
1291		447/48	carcinoma stomach ; lung abscess, empyema (1)
1292		508/49	carcinoma tongue ; myocardial infarct (1)
1293		368/47	pyaemia (1)
1294		467/47	carcinoma breast ; peritonitis (1)
1295		449/47	generalised dermatitis ; healed myocardial infarct (1)
1296		421/47	strangulated inguinal hernia ; myocardial infarcts ; thrombo-angiitis obliterans (1)
1297		149/47	meningiomata ; pulmonary embolism (1)
1298		500/46	peptic ulcers, haemorrhage (1)
1299		502/46	appendicitis, peritonitis (1)
1300		525/46	astrocytoma (1)
1301		535/46	fractured femur ; senile hyper-plasia prostate (1)
1302		498/46	appendicitis, peritonitis (1)
1303		468/46	gastric ulcer, peritonitis, neurofibromatosis (1)
1304		459/46	nephrosclerosis, uraemia (1)
1305		375/46	nephritis (1)
1306		329/46	burns ; pulmonary oedema (1)
1307		325/46	pancreatic necrosis (1)
1308		242/47	? diphtheria, myocardial degeneration; pyelonephritis (1)
1309		133/48	myxoedema ; nephrosclerosis (1)
1310		213/48	Hodgkin's disease : cirrhosis liver (1)
1311		593/47	hydatid disease (1)
1312	MHA	2106	miliary tuberculosis (1)
1313		2162	prematurity (1)
1314		2292	disseminated sclerosis ; nephrosclerosis (1)
1315		2299	postencephalitic Parkinsonism; bronchopneumonia (1)
1316		2301	nephrosclerosis, cerebral infarcts (1)
1317		2309	malignant nephrosclerosis (1)
1318		2512	poliomyelitis (1)
1319	PM	32/42	ruptured aneurysm middle colic artery (1)
1320		99/48	carcinoma thyroid ; gastric ulcer ; pulmonary embolism (4)
1321		96/48	hernia, cellulitis abdominal wall(2)

1322/

1322	PM	102/48	carcinoma bronchus ; nephrosclerosis (4)
1323		115/48	myocardial infarcts ; senile hyperplasia prostate (3)
1324		101/48	nephrosclerosis ; mesenteric thrombosis (3)
1325		130/48	abortion, recto-vagino-vesical fistula, pyelitis (4)
1326		142/48	syphilis ; nephrosclerosis, uraemia (3)
1327		143/48	duodenal ulcer, diverticulitis; nephrosclerosis (3)
1328		88/48	nitric acid poisoning (1)
1329		495/47	tuberculous bronchopneumonia (1)
1330		577/47	cholecystitis, peritonitis (1)
1331		554/47	lobar pneumonia, sinusitis, meningitis (1)
1332		602/47	carcinoma breast ; tuberculosis ovary (1)
1333		606/47	carcinoma bronchus, bronchiectasis, lung abscess (1)
1334		30/48	duodenal ulcer, peritonitis (1)
1335	MHA	2605	lobar pneumonia, lung abscess (1)
1336	LII/	2143	pernicious anaemia (1)
1337	PM.	39/47	senile hyperplasia prostate ; nephrosclerosis (3)
1338		531/47	carcinoma breast (3)
1339		123/48	leiomyosarcoma jejunum ; abscesses liver and brain (3)
1340		527/48	carcinoma bronchus (3)
1341		109/48	carcinoma stomach (4)
1342		122/48	carcinoma bronchus ; duodenal ulcer (3)
1343	EHA	904	epilepsy (3)
1344	PM	116/48	myocardial and pulmonary infarcts; focal necrosis liver (4)
1345		108/48	glomerulonephritis ; pyogenic infection kidneys (5)
1346		110/48	carcinoma pancreas ; senile hyperplasia prostate (4)
1347		429/50	viral hepatitis, liver failure (4)
1348	XLI/	474	trichiniasis (2)
1349	MHA	3448	malnutrition (2)
1350		3039	nephrosclerosis ; bronchopneumonia (4)
1351		3041	bronchiectasis, lung abscess, empyema (4)
1352		3049	senile hyperplasia prostate ; pulmonary embolism ; myocarditis (4)
1353	EHA	866	bronchiectasis, bronchopneumonia ; anaemia (4)
1354	MHA	3066	duodenal ulcer, peritonitis, pyaemia (4)
1355		3067	tonsillectomy, haemorrhage (4)
1356		3075	nephrosclerosis, cerebral infarcts (4)

1357/

1357	MHA	3076	biliary cirrhosis, hepatorenal failure (5)
1358	EHA	890	carcinoma kidney (4)
1359	MHA	3104	purulent trachec-bronchitis ; nephrosclerosis (4)
1360		3105	staphylococcal bronchopneumonia and septicaemia (4)
1361		3109	inhaled vernix, atelectasis, pneumonia (4)
1362		3110	duodenal ulcer, peritonitis; bronchiectasis ; pyelonephritis (5)
1363		3112	bronchitis, emphysema, cardiac failure (4)
1364		3113	syphilitic aortitis ; pulmonary infarct (5)
1365		3119	hydrocephalus ; inhaled liquor amnii (4)
1366		3120	nephrosclerosis, uraemia (3)
1367		3129	strangulated femoral hernia (4)
1368		3130	renal scarring ; cerebral infarct (4)
1369		3172	bronchopneumonia ; cardiac failure (4)
1370	PM	316/49	myasthenia gravis, asphyxia (6) (Fig. 188).
*1371			amyotrophic lateral sclerosis (1)
1372	PM	380/49	cut throat (5)
1373		385/49	carcinoma gall bladder, peritonitis (5)
1374	MHA	2808	carcinoma bronchus, empyema (4)
1375		2810	intracerebral haemorrhage ; staphylococcal pneumonia (4)
1376		1968	asphyxia (1)
1377	PM	492/49	multiple injuries ; pulmonary embolism (5)
1378	MHA	3268	viral hepatitis, cirrhosis liver, carcinoma cervix (3)
1379		2710	tuberculosis bronchopneumonia ; malignant cholangioma ; nephrosclerosis (3)
1380		2722	carcinoma pancreas, peritonitis (4)
1381		2736	nephrosclerosis ; cirrhosis liver (3
1382	PM	287/48	acute hepatitis ; retrobulbar neuritis (5)
1383		534/47	duodenal ulcer, carcinoma, peritonitis (2)
1384		25/49	? allergic lesions spleen and lymph nodes ; serositis, nephrosclerosis (7) (Fig. 159)
1385	MHA	3127	appendicitis, peritonitis (5)
1386	EHA	896	gastric ulcer ; post-operative collapse of lung (4)
1387	PM	14/49	burns ; stenosis of aqueduct (2)
1388		68/49	bronchitis ; cardiac failure (2)
1389		89/49	bronchiectasis ; gastric ulcer (4)
1390		113/49	bronchopneumonia (2)
1391		176/49	malignant nephrosclerosis ; bronchopneumonia (3)
1392		196/49	carcinoma uterus (1)
1393		246/49	nephrosclerosis, cerebral haemorrhage (1)

1394/

1394	PM	127/50	multiple injuries, fat embolism (5)
1395		179/50	carcinoma stomach ; renal calculus (4) (Fig. 185)
1396		13/48	tuberculous cystitis and peritonitis (1)
1397		71/48	pulmonary embolism (following pelvic floor repair) (3)
1398		178/48	exfoliative dermatitis ; focal granulomata heart and lungs (3)
1399		233/48	myxoedema ; nephrosclerosis (1)
1400		432/48	carcinoma colon, peritonitis (4)
1401		468/48	rupture of cerebral aneurysm ; herpes ophthalmica (2)
1402		536/48	nephrosclerosis ; phlebothrombosis legs, paradoxical embolism, infarcts brain, kidneys and intestine (2)
1403		49/49	gastro-colic fistula (3)
1404		118/49	pernicious anaemia (1)
1405		468/49	multiple injuries (2)
1406		482/49	malignant nephrosclerosis, cerebral haemorrhage (4)
1407		643/49	bronchitis, bronchopneumonia; haemorrhagic nephritis (2)
1408		595/47	appendicitis, peritonitis (2)
1409		557/47	staphylococcal pyaemia (3)
1410		533/47	sulphonamide hypersensitivity reactions (4)
1411		338/47	progressive muscular atrophy ; pneumonia (2)
1412		220/47	? diphtheritic myocarditis ; transfusion haemolysis (2)
1413		106/47	malignant nephrosclerosis (2)
1414		562/46	multiple injuries (3)
1415		465/46	multiple injuries (2)
1416		317/46	malignant nephrosclerosis, cardiac failure (2)
1417		301/46	fractured femur (3)
1418		258/46	lobar pneumonia (2)
1419		232/46	multiple injuries (2)
1420		173/46	rectal abscess ; cardiac failure (2)
1421		128/46	malignant nephrosclerosis, uraemia (2)
1422		305/46	organising pneumonia ; glomerulonephritis (2)
1423		507/46	pernicious anaemia (1)
1424	MHA	2122	carcinoma pancreas
1425		2311	Friedreich's ataxia ; cardiac failure (2)
1426		2625	multiple injuries (2)
1427		3151	carcinoma bronchus (2)
1428	PM	258/48	bronchiectasis, anthracosis ; cardiac failure (3)
1429		134/38	diabetes mellitus ; myocardial infarct ; nephrosclerosis (1)
1430		548/47	gastric ulcer, haemorrhage ; senile hyperplasia prostate (3)
1431		549/47	carcinoma rectum ; colloid goitre (2)

1432/

1432	PM	585/47	glioblastoma, multiforme ; nephrosclerosis ; pancreatic necrosis (2)
1433		63/48	normal 4½ months foetus (3)
1434		74/48	cirrhosis liver ; organising pneumonia (3)
1435		75/48	ureteral calculi, pyonephrosis, peritonitis (2)
1436		71/48	multiple injuries (3)
1437		92/48	carcinoma prostate ; pyelonephrisis (4)
1438		93/48	squamous carcinoma with extensive metastasis (3)
1439		94/48	carcinoma bronchus ; pyelitis (6)
1440		146/48	carcinoma prostate ; anthracosilicosis (3)
1441		147/48	carcinoma stomach (2)
1442		148/48	? traumatic cerebellar haemorrhage (3)
1443		154/48	carcinoma bronchus (4)
1444		190/48	peptic ulcer, postoperative haemorrhage (3)
1445		314/50	multiple injuries, fat embolism (5)
1446		127/51	Mikulicz disease (2)
1447	XLV/	943	hypertension (1)
1448	L /801		temporal arteritis (1)
1449	PM	421/50	lobar pneumonia ; tuberculosis kidney (3)
1450		423/50	carcinoma bronchus ; pulmonary infarction (3)
1451		424/50	carcinoma colon, perforation, peritonitis (5)
1452		425/50	anthracosilicosis, cardiac failure (3)
1453		428/50	miliary tuberculosis (3)
1454		430/50	carcinoma colon ; pulmonary tuberculosis (3)

SECTION V.

The following cases which were used in this Section have been listed previously :-

Case 925 - under Section I
Case 1037 - under Section III
Cases 1112, 1116, 1119-1122, 1126, 1179, 1224, 1257, 1263, 1265, 1267, 1281-1283, 1296, 1337, 1338, 1340, 1383, 1384, 1395, 1430-1432, 1445 - under Section IV.

In the following cases, the major pathological lesions are noted, also the number of blocks taken (in brackets) :-

Case	Ref :	
1455	PM. 101/50	nephrosclerosis, cardiac failure (6)
1456	89/50	bronchiectasis ; amyloidosis (6)
1457	92/50	carcinoma breast ; septic infarcts lungs (3)
1458	93/50	lobar pneumonia (6)

1459/

1459	PM. 94/50	carcinoma stomach ; empyema ; carcinoma kidney (6)
1460	95/50	carcinoma bronchus ; cirrhosis liver (6)
1461	99/50	nephrosclerosis, cerebral haemorrhage (6)
1462	100/50	duodenal ulcer, peritonitis (6)
1463	102/50	staphylococcal bronchopneumonia (6)
1464	154/50	myocardial infarcts (6)
1465	181/50	bilateral tubo-ovarian abscess, peritonitis (6)
1466	183/50	malignant neoplasm caecum ; pulmonary embolism (6)
1467	186/50	emphysema ; nodular hyperplasia liver (6)
1468	105/50	bronchiectasis ; cardiac failure (6)
1469	106/50	appendicitis, peritonitis (6)
1470	108/50	nephrosclerosis ; myocardial infarcts (6) (Fig. 183)
1471	110/50	carcinoma stomach ; pulmonary embolism (6)
1472	119/50	aortic stenosis ; bronchopneumonia (6)
1473	120/50	senile hyperplasia prostate ; renal cortical necrosis (6)
1474	138/50	bronchitis, emphysema ; cardiac failure (6)
1475	170/50	status epilepticus ; haemothorax (6)
1476	169/50	carcinoma bronchus, lung abscesses (6)
1477	173/50	myocardial infarcts (6)
1478	174/50	gastric ulcer, post-operative shock (6)
1479	176/50	influenzal bronchopneumonia (6)
1480	175/50	nephrosclerosis, cardiac failure (6)
1481	177/50	pyonephrosis (6)
1482	178/50	carcinoma liver (6)
1483	163/50	cerebral infarcts (6)
1484	144/50	senile hyperplasia prostate ; bronchitis (6)
1485	145/50	influenzal bronchopneumonia (6)
1486	159/50	carcinoma stomach ; lung abscess; tuberculous lymphadenitis (6)
1487	162/50	pernicious anaemia ; pulmonary embolism (6)
1488	164/50	bronchopneumonia ; tension pneumothorax (6)
1489	126/50	carbon monoxide poisoning ; aspiration pneumonia (6)
1490	127/50	multiple injuries, fat embolism (6)
1491	140/50	post-transfusion anuria (6)
1492	160/50	carcinoma bladder ; renal cortical necrosis (6)
1493	143/50	dissecting atheromatous aneurysm aorta (6)
1494	529/47	bronchiectasis ; senile hyperplasia prostate (4)
1495	187/50	myocardial infarcts (6)
1496	188/50	carcinoma stomach ; pyonephrosis (6)
1497	189/50	mastoiditis, meningitis, cerebral abscess (6)

1498/

1498	PM	197/50	intestinal obstruction ; pyelonephritis (6)
1499		198/50	silicosis ; cardiac failure (6)
1500		199/50	nephrosclerosis ; cerebral infarct ; cardiac failure (6) (Fig. 203)
1501		202/50	carcinoma colon ; renal infarct ; silicosis (6)
1502		203/50	carcinoma gall bladder (6)
1503		204/50	cerebral haemorrhage (6)
1504		205/50	carcinoma rectum ; pyelitis, cystitis (6)
1505		312/50	pneumonia, empyema ; syphilitic aortitis (6)
1506		313/50	nephrosclerosis ; cerebral haemorrhage (6)
1507		322/50	myocardial infarction (6)
1508		323/50	strangulated femoral hernia ; pulmonary embolism (6)
1509		324/50	volvulus ; gastric ulcer (6)
1510		384/50	pontine infarct (6)
1511		374/50	carcinoma bronchus (6)
1512		399/50	carcinoma breast ; liver failure (6)
1513		377/50	carcinoma bronchus ; liver failure (6)
1514		392/50	barbiturate poisoning ; carcinoma liver ; myocardial infarct (6)
1515		360/50	myocardial infarct ; pyelonephritis (6)
1516		328/50	myocardial infarct (6)
1517		389/50	reticulosarcoma ; pulmonary infarcts (6)
1518		391/50	gastric ulcer, perforation, peritonitis (6)
1519		388/50	pyelonephritis ; hydatid disease liver (6)
1520		387/50	peptic ulcer, peritonitis (6)
1521		405/50	cerebral infarcts (6)
1522		383/50	carcinoma rectum ; uraemia (6)
1523		370/50	carcinoma prostate ; cerebral infarcts (3)
1524		344/50	tuberculous bronchopneumonia and colitis (6)
1525		359/50	bronchopneumonia (3)
1526		385/50	renal hypoplasia, hypertension (6)
1527		372/50	arthracosilicosis ; senile hyperplasia prostate (6)
1528		394/50	anthracosilicosis ; carcinoma bronchus (6)
1529		369/50	carcinoma pancreas ; bronchisis (2)
1530		371/50	nephrosclerosis ; gangrene leg (6)
1531		376/50	carcinoma stomach ; Wernicke's encephalopathy (6)
1532		403/50	cholecystitis, hepatic abscesses, peritonitis (6)
1533		343/50	staphylococcal pyaemia ; diabetes mellitus (6)

1534/

1534	PM.	361/50	intestinal obstruction ; aspiration pneumonia (6)
1535		345/50	cholecystitis ; pulmonary embolism (6)
1536		408/50	mesenteric thrombosis, infarct intestine, peritonitis (6)
1537		419/50	nephrosclerosis, cardiac failure (6)
1538		412/50	carcinoma stomach (6)
1539		410/50	carcinoma breast (6)
1540		395/50	status epilepticus ; broncho-pneumonia (6)
1541		411/50	multiple injuries (6)
1542		417/50	alcoholic intoxication (6)
1543		418/50	carcinoma bronchus (6)
1544		409/50	multiple injuries (6)